



GP-OSMOTIC trial protocol: an individually randomised controlled trial to determine the effect of retrospective continuous glucose monitoring (r-CGM) on HbA1c in adults with type 2 diabetes in general practice

Citation:

Furler, John, O'Neal, David Norman, Speight, Jane, Blackberry, Irene, Manski-Nankervis, Jo-Anne, Thuraisingam, Sharmala, de La Rue, Katie, Ginnivan, Louise, Browne, Jessica Lea, Holmes-Truscott, Elizabeth, Khunti, Kamlesh, Dalziel, Kim, Chiang, Jason, Audehm, Ralph, Kennedy, Mark, Clark, Malcolm, Jenkins, Alicia Josephine, Liew, Danny, Clarke, Philip and Best, James 2018, GP-OSMOTIC trial protocol: an individually randomised controlled trial to determine the effect of retrospective continuous glucose monitoring (r-CGM) on HbA1c in adults with type 2 diabetes in general practice, *BMJ open*, vol. 8, no. 7, article ID: e021435, pp. 1-10.

DOI: <http://www.dx.doi.org/10.1136/bmjopen-2017-021435>

©2018, The Authors

Reproduced by Deakin University under the terms of the [Creative Commons Attribution Non-Commercial Licence](#)

Downloaded from DRO:

<http://hdl.handle.net/10536/DRO/DU:30111683>

BMJ Open GP-OSMOTIC trial protocol: an individually randomised controlled trial to determine the effect of retrospective continuous glucose monitoring (r-CGM) on HbA1c in adults with type 2 diabetes in general practice

John Furler,¹ David Norman O'Neal,² Jane Speight,^{3,4} Irene Blackberry,⁵ Jo-Anne Manski-Nankervis,¹ Sharmala Thuraingam,¹ Katie de La Rue,¹ Louise Ginnivan,¹ Jessica Lea Browne,^{3,4} Elizabeth Holmes-Truscott,^{3,4} Kamlesh Khunti,⁶ Kim Dalziel,⁷ Jason Chiang,¹ Ralph Audehm,¹ Mark Kennedy,¹ Malcolm Clark,¹ Alicia Josephine Jenkins,⁸ Danny Liew,⁹ Philip Clarke,¹⁰ James Best¹¹

To cite: Furler J, O'Neal DN, Speight J, *et al*. GP-OSMOTIC trial protocol: an individually randomised controlled trial to determine the effect of retrospective continuous glucose monitoring (r-CGM) on HbA1c in adults with type 2 diabetes in general practice. *BMJ Open* 2018;**8**:e021435. doi:10.1136/bmjopen-2017-021435

► Prepublication history and additional material for this paper are available online. To view these files, please visit the journal online (<http://dx.doi.org/10.1136/bmjopen-2017-021435>).

Received 3 January 2018
Revised 24 May 2018
Accepted 1 June 2018



© Author(s) (or their employer(s)) 2018. Re-use permitted under CC BY-NC. No commercial re-use. See rights and permissions. Published by BMJ.

For numbered affiliations see end of article.

Correspondence to

Dr John Furler;
j.furler@unimelb.edu.au

ABSTRACT

Introduction Optimal glycaemia can reduce type 2 diabetes (T2D) complications. Observing retrospective continuous glucose monitoring (r-CGM) patterns may prompt therapeutic changes but evidence for r-CGM use in T2D is limited. We describe the protocol for a randomised controlled trial (RCT) examining intermittent r-CGM use (up to 14 days every three months) in T2D in general practice (GP).

Methods and analysis General Practice Optimising Structured Monitoring To achieve Improved Clinical Outcomes is a two-arm RCT asking 'does intermittent r-CGM in adults with T2D in primary care improve HbA1c?'

Primary outcome Absolute difference in mean HbA1c at 12 months follow-up between intervention and control arms. Secondary outcomes: (a) r-CGM per cent time in target (4–10 mmol/L) range, at baseline and 12 months; (b) diabetes-specific distress (Problem Areas in Diabetes).

Eligibility Aged 18–80 years, T2D for ≥1 year, a (past month) HbA1c >5.5 mmol/mol (0.5%) above their individualised target while prescribed at least two non-insulin hypoglycaemic therapies and/or insulin (therapy stable for the last four months). Our general glycaemic target is 53 mmol/mol (7%) (patients with a history of severe hypoglycaemia or a recorded diagnosis of hypoglycaemia unawareness will have a target of 64 mmol/mol (8%)). Our trial compares r-CGM use and usual care. The r-CGM report summarising daily glucose patterns will be reviewed by GP and patient and inform treatment decisions. Participants in both arms are provided with 1 hour education by a specialist diabetes nurse. The sample (n=150/arm) has 80% power to detect a mean HbA1c difference of 5.5 mmol/mol (0.5%) with an SD of 14.2 (1.3%) and alpha of 0.05 (allowing for 10% clinic and 20% patient attrition).

Ethics and dissemination University of Melbourne Human Ethics Sub-Committee (ID 1647151.1). Dissemination will be

Strengths and limitations of this study

- Our study uses the latest glucose monitoring technology available to optimise collaborative management of type 2 diabetes (T2D) to achieve timely intensification of therapy with minimal monitoring burden for the person with T2D.
- Our pragmatic, individually randomised controlled trial will produce robust data about the effectiveness of using retrospective continuous glucose monitoring as an adjunct to HbA1c at 3-monthly intervals, in primary care.
- Our trial is occurring in Victoria, Australia, and so may have limited applicability to countries with different primary care systems.
- Despite individual randomisation, potential contamination between study arms will be minimised as the amount of glucose data available to general practitioners in managing intervention and control group participants will differ significantly.
- The collection of a range of patient-reported outcome measures and a planned qualitative study will enable robust process evaluation.

in peer-reviewed journals, conferences and a plain-language summary for participants.

Trial registration number >ACTRN12616001372471; Pre-results.

BACKGROUND

Introduction

Type 2 diabetes (T2D) is a leading cause of disease burden, doubling in prevalence in the last 20 years and costing the global community

an estimated US\$376 billion in 2010.¹ Much of this money is spent on lowering blood glucose levels and managing complications. Achieving and sustaining glycaemic targets is important in reducing downstream complications (particularly microvascular) and all-cause mortality.² Yet most people with T2D do not achieve or sustain target glycated haemoglobin (HbA1c—an index of average blood glucose level over the preceding 12 weeks),³ despite a growing range of available medications.⁴ Clinical care in general practice can help people achieve glycaemic targets,⁵ through adoption of an evidence-based ‘treat to target’ approach (step-wise treatment intensification through changes to lifestyle, medication doses and/or prescription of additional medications) as recommended by guidelines internationally.^{6–8}

A number of factors influence timely treatment intensification.⁹ These include the knowledge, skills and motivation of both general practitioners (GPs) and people with T2D. Both may be concerned by the challenges of deciding on and managing complex treatment regimens. For GPs, ‘clinical inertia’ may also be fuelled by concerns about hypoglycaemia,¹⁰ while many people with T2D experience ‘psychological insulin resistance’, including feelings of failure, to the extent that one in four would be unwilling to use insulin if it were recommended.¹¹

Current guidelines base treatment intensification recommendations on HbA1c levels,^{12–13} and several studies have determined there are minimal clinical benefits of routine ‘finger-prick’ glucose monitoring.^{14–15} Indeed, several countries, including Australia, have now restricted the subsidy of blood glucose test strips for people with T2D not using insulin.¹⁶ However, HbA1c alone may not provide sufficient information to guide personalised decisions about treatment intensification. Identifying day-to-day glucose profiles could supplement HbA1c, building both the knowledge and skills of clinicians and people with T2D, providing motivation for treatment intensification, as well as addressing any underlying concerns about risk for hypoglycaemia. Random, ad hoc glucose measurements do not provide sufficient detail to identify such glucose profiles.¹⁶

Manual structured self-monitoring of blood glucose (S-SMBG), where people with T2D record blood glucose levels intensively over a short period of time (at set times or in relation to key moments, eg, pre/post meals or physical activity), can enable GPs and people with T2D to identify meaningful glucose profiles.¹⁷ One trial tested S-SMBG used on a 3-monthly basis in people with T2D managed in primary care in the USA, identifying clinically significant improvements in glycaemia on a per-protocol analysis,¹⁸ accompanied by increased confidence in self-care.¹⁹ However, nearly 50% of participants either withdrew or did not adhere to the manual monitoring protocol,¹⁸ suggesting the intensive finger-pricking required (eg, seven times per day for three consecutive days) can be a barrier to the real-world implementation of S-SMBG. To personalise treatment intensification, clinicians and people with T2D need a simple, acceptable, feasible, reliable and effective method of identifying glucose profiles.

Continuous glucose monitoring (CGM) is another method of identifying glucose profiles. CGM involves measuring glucose levels continuously using an enzyme-coated wire or filament inserted into the subcutaneous tissue. CGM measures interstitial glucose levels through generation of an electrical current when glucose reacts with the enzyme glucose oxidase. Until recently, CGM technology has calibrated this electrical current to glucose levels through finger-prick measurements on several occasions during the day. Recent advances in factory-calibrated technology mean that finger-prick measurements are not needed for some CGM devices. While originally licensed only for adjunctive use, increasingly CGM is being licensed around the world for making treatment decisions, such as adjustment of insulin doses.

CGM can either be used in real time or retrospectively (also known as personal or professional modes). Retrospective CGM (r-CGM) involves the patient wearing a CGM sensor for a period of up to 2 weeks with the glucose data downloaded and reviewed retrospectively in collaboration with their health professional, to identify day-to-day glucose profiles to guide treatment decisions. For many people with T2D, glucose profiles tend to be reproducible on a day-to-day basis. For these people, intermittent, r-CGM may be an appropriate tool for informing management decisions. The use of r-CGM, particularly when no finger-prick calibration is involved, minimises the burden of monitoring and may overcome a key barrier to engagement. r-CGM can also provide detail about hypoglycaemia and hyperglycaemia, as well as time spent in target range, which are all important to clinical and psychosocial outcomes for people with T2D.²⁰ Evidence suggests that unrecognised hypoglycaemia is not uncommon among people with T2D.²¹ Finally, r-CGM can provide insight into glycaemic variability (GV), that is, the extent to which glucose fluctuates throughout the day. There is growing interest in targeting reduced GV as an independent clinical goal with potential to reduce complication rates.²²

For people with T2D, r-CGM thus offers the prospect of an advance in appropriate and personalised care.²³ However, the evidence base for its use in T2D is currently limited, with mixed findings. Two trials of real-time CGM (ie, unblinded) have been conducted in a select population of adults with T2D using multiple daily injections of insulin: neither resulted in a clinically significant improvement in HbA1c, and while one reduced hypoglycaemia and improved treatment satisfaction, the other did not.^{24–25} A retrospective matched cohort study did identify an improvement in HbA1c associated with use of r-CGM (ie, blinded) and called for large-scale prospective randomised controlled trials (RCTs) to provide definitive evidence.²⁶ A small number of RCTs suggest that r-CGM is potentially effective in people with T2D using both insulin and non-insulin therapy regimens in achieving glycaemic targets. However, these trials are generally small in sample size, ranging from 25 to 52 people,²⁷ with short follow-up periods of 3–6 months.^{27–28} A recently published observational study in India also showed promise in r-CGM for

people with T2D, but with only 148 participants, a short 3-month follow-up period and the possibility of selection bias in a non-randomised study, the results need to be interpreted with caution.²⁹ Thus, preliminary evidence from small RCTs and observational studies suggests the potential efficacy of r-CGM in people with non-insulin-treated T2D, but larger adequately powered RCTs are needed to study its effectiveness.

Importantly, glucose monitoring, whether manual or through new technologies, is not an end in itself. Indeed, technology can become burdensome to people with T2D.³⁰ Rather, how the information is understood and used is central to its utility, and this requires appropriate education of both the health professional and the person with T2D.^{30 31} Use of r-CGM needs to be undertaken collaboratively between patient and GP, with support from Credentialed Diabetes Educators (CDE) and endocrinologists as appropriate. Active participation of the person with T2D in this discussion may lead to improved understanding and interpretation of glucose patterns, informed by the individual's reflection on their lifestyle habits, as well as improving their understanding of the rationale for treatment intensification to achieve glycaemic targets.³¹ Indeed, prior research suggests that understanding of and engagement with glucose patterns among people with T2D may be a facilitator of treatment intensification.^{19 32} Both the GP and person with T2D need training to interpret the data, to work collaboratively to plan lifestyle or medication changes and set appropriate goals. The person with T2D needs the behavioural skills to make changes to self-management, and GPs need to work in partnership with them to support self-management. To do so, GPs also need to understand the importance of glycaemic targets and have the skills and confidence to interpret glucose patterns, make appropriate treatment changes and have collaborative discussions with the patient about active self-management of T2D. None of the studies outlined above include substantial educational components of this nature.

Aim and research questions

Our aim is to conduct an individually RCT to examine the effectiveness of the intermittent use of r-CGM in the management of T2D in general practice, and specifically to test the effect of r-CGM on achieving glycaemic targets.

Our research questions are

1. Does the judicious use of intermittent r-CGM in people with T2D in primary care improve glycaemic control as measured by HbA1c?
2. Is intermittent r-CGM cost-effective?

METHODS AND ANALYSIS

Study design

GP-OSMOTIC is a two-arm individually RCT in general practice comparing collaborative use of r-CGM to usual care in people with T2D whose HbA1c is above recommended target, despite prescription of at least two

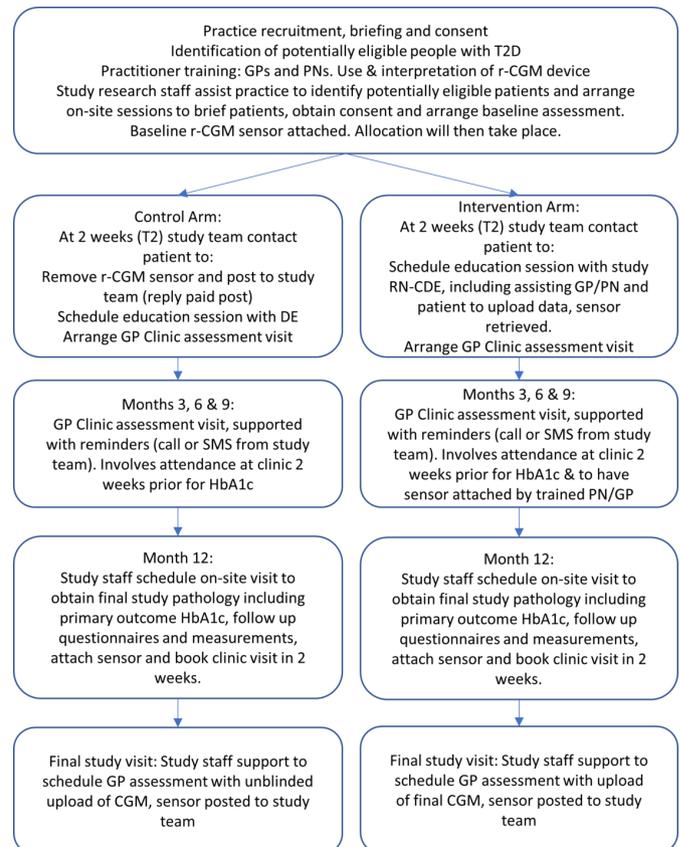


Figure 1 Study Consolidated Standards of Reporting Trials design. GP, general practitioner; r-CGM, retrospective continuous glucose monitoring; RN-CDE, Registered Nurse-Credentialed Diabetes Educator; T2D, type 2 diabetes.

non-insulin hypoglycaemic agents and/or insulin. The study design is outlined in the Consolidated Standards of Reporting Trials (CONSORT) diagram (figure 1). Reporting will follow CONSORT guidelines for RCTs.^{33 34}

Participant recruitment and randomisation procedures

Practices with at least one consenting GP are eligible. Practices will be approached from a database of research and teaching active practices associated with the Department of General Practice at the University of Melbourne.

Eligible patients will be aged 18–80 years, active patients of the practice (defined as three or more visits to the practice in the past two years), have had T2D for at least 1 year with their most recent HbA1c (in the previous one month) ≥ 5.5 mmol/mol (0.5%) above their individualised target (see below), while prescribed at least two non-insulin hypoglycaemic agents as therapy and/or insulin (therapy stable for the past four months). Our general glycaemic target is set at 53 mmol/mol (7%), while those with a history of severe hypoglycaemia (requiring assistance from a third person for recovery) or a recorded diagnosis of hypoglycaemia unawareness will have a target of 64 mmol/mol (8%), consistent with Australian guidelines.³⁵ In the setting of this pragmatic trial, we will allow GPs to indicate a personalised target

for a participant if they feel that it should differ from the two prespecified targets set out above.

Patient exclusion criteria will include any debilitating medical condition (eg, unstable cardiovascular disease, severe mental illness, end-stage cancer), an electronic Glomerular Filtration Rate <30; proliferative retinopathy, pregnancy, lactating or planning pregnancy, unable to speak English/give informed consent, unwilling to use r-CGM or follow study protocol, allergy to adhesive tape, any condition that makes monitoring of glucose control using HbA1c unreliable (eg, haemoglobinopathy, iron deficiency anaemia).

Practices that agree to participate will be asked to generate a list of potentially eligible patients to be screened for full eligibility by searching their practice electronic medical record database. Patients will then be invited by letter and/or telephone call to attend the practice to hear more about the study and give consent. At this visit, a clinically trained research assistant will explain the study and, if the patient consents, collect baseline demographic, clinical, biometric and psychometric data and arrange baseline pathology tests. Study data will be collected and managed using REDCap³⁶ electronic data capture tools hosted at the University of Melbourne. Final eligibility will be confirmed based on the baseline HbA1c.

The remaining list of consenting eligible participating patients will be randomly allocated to intervention or control using an electronic radio-button in REDCap. Electronic contact is made with an allocation schedule developed and held at the University of Melbourne Department of General Practice. Patients will not be allocated until after study consent is obtained, baseline data collected, eligibility confirmed and baseline r-CGM trace is started (ie, sensor attached). Participant timeline is provided as online supplementary appendix 1.

We will use block randomisation at the practice level, that is, block randomisation sequences of 4 and 6 will be computer generated by the study statistician for each practice who participate and individual participating patients at each practice site will be randomised.

Participant recruitment commenced in October 2016 and was completed in October 2017. Final 12-month follow-up is anticipated to be completed in October 2018.

Intervention description

The General Practice Optimising Structured MOonitoring To achieve Improved Clinical Outcomes (GP-OSMOTIC) intervention is informed by the existing evidence for structured SMBG^{20 37} and our understanding that the effective application of glucose monitoring is just one aspect of a complex behavioural intervention, including but not limited to clinician/patient agreement and motivation for monitoring; establishment of glucose targets and parameters for monitoring (timing/frequency/duration); interpretation of glucose patterns; action planning (for how to intervene to improve glucose levels); action (eg, changing food/drink, physical activity and/or medication); and monitoring and reflection.³⁸ Drawing on

this literature, health professionals will be encouraged to employ our 'Check, Chat, Change (repeat)' framework within the consultation with intervention participants with T2D (table 1). This framework aims to build motivation, confidence and skills of participating health professionals and people with T2D in the collaborative use of r-CGM, interpretation of glucose patterns and intervention to improve glucose levels.

The desired 'Check, Chat, Change' training components and outcomes described in table 1 are delivered via a 2 hour training session, for all participating GPs and practice nurse (PN), either on site at the practice or via an online video recording of the training. The training is delivered by a GP with a special interest in T2D and a Registered Nurse-Credentialed Diabetes Educator (RN-CDE) with minimum 5 years' experience. The training content is developed by the GP and RN-CDE, with input from health psychologists with expertise in diabetes self-management and education (JS and JB). Throughout the training session, GPs and PNs will have opportunity to reflect on their attitudes towards glucose monitoring in T2D, test their knowledge about how to apply the r-CGM device, review r-CGM trace data and identify suitable treatment change options.

Participating people with T2D randomised to the intervention arm will attend an individual face-to-face diabetes education session of 60 min with the study RN-CDE. This will be held on site at the patient's general practice. This session will include instruction on how to wear the r-CGM device and how to interpret the glucose reports from the device to better understand their blood glucose and how this relates to their diabetes self-management and treatment options. Brief supportive information about the device and about diabetes self-management (as commonly provided in diabetes education sessions) will be provided to patients by the GP clinic staff and the study CDE. Participating GPs also have the opportunity to sit in and observe this session with the first patient randomised to the intervention arm.

Intervention participants will be asked to wear the r-CGM device for a period of 2 weeks every three months, that is, at baseline, 3, 6, 9 and 12 months, as well as having an HbA1c taken at those times, and to attend a consultation with their GP and discuss the r-CGM reports. This 3-monthly interval is consistent with clinical practice guidelines about regular, stepwise consideration of treatment intensification. The r-CGM device will be applied at those 3-monthly intervals at the GP clinic (ie, by the GP or PN who have attended the health professional training). Patients and practices will be sent reminders to undertake this 3-monthly monitoring.

Those randomised to the control group will wear the r-CGM device at baseline but the data will be blinded to both the patient participant and their GP. They will continue to receive usual clinical care. Both GP and patient will, however, be prompted to undertake 3-monthly diabetes reviews consistent with clinical practice guidelines about regular stepwise consideration of

Table 1 The 'Check, Chat, Change' framework and training elements

| | Target outcome/behaviour | Health professional training |
|------------------|--|---|
| Check | GP understanding of evidence for effective and timely assessment of blood glucose and using r-CGM Effective and timely assessment of blood glucose using r-CGM Engagement of person with T2D in collaborative consultation | Present evidence and rationale for treatment intensification Present information about and demonstrate (model) how to apply/remove sensors, download and interpret r-CGM data; support person with T2D in correct use of r-CGM as a complement to usual care and testing Demonstrate (model) collaborative engagement of person with T2D in use of r-CGM |
| Chat | Collaborative reflection on and interpretation of recurring glucose patterns, and the effect of food/drink, physical activity and medication | Present information about how to read and interpret r-CGM patterns Demonstrate interpretation of r-CGM patterns by GP and RN-CDE using case studies Demonstrate (model) collaborative engagement of person with T2D in the interpretation of r-CGM, supporting them to interpret glucose patterns, identifying hyperglycaemia and hypoglycaemia and impact of lifestyle and medications on glucose levels |
| Change | Identify appropriate intervention to improve blood glucose and engage person with T2D in action planning | Present evidence (clinical guidelines) for intensification of lifestyle, OHA, injectable medications in response to r-CGM Demonstrate (model) collaborative discussion of potential change in management of T2D and agreement on action plan |
| Repeat the cycle | Observe and reflect on the effectiveness of changes made at the next visit | |

GP, general practitioner; OHA, Oral Hypoglycaemic agent; r-CGM, retrospective continuous glucose monitoring; RN-CDE, Registered Nurse-Credentialed Diabetes Educator; T2D, type 2 diabetes.

treatment intensification. Participants randomised to the control group will also attend an education session with a local CDE (funded by the study if necessary to eliminate financial barriers). We will assist with scheduling this for control group.

Regardless of the study arm to which their patients are randomised, the GP will be free to refer to or consult with an endocrinologist, CDE or any other appropriate health professional, as part of their usual clinical practice.

r-CGM device to be used in the study

The r-CGM device being used in the study is the Abbott *FreeStyle Libre Pro Flash Glucose Monitoring System*. The system has three parts: a hand-held reader, a disposable sensor and associated software. The sensor is applied to the upper arm of the person with T2D by the health professional (eg, GP or PN) and activated using the reader. The sensor is worn by the person with T2D for up to 14 days, over which time it records interstitial glucose levels every 15 min, though these readings are not visible to the person wearing the sensor. No additional finger-prick calibration is needed. At any time, the person can return to their health professional to have data from the sensor uploaded via the reader to software on a computer, although at least 5 days of data is needed to generate meaningful output.^{39 40} Using the reader, the health professional downloads the glucose data from the sensor in the form of reports summarising daily patterns of glucose levels, called an 'ambulatory glucose profile' (AGP). These are then used to identify glucose patterns,

including hypoglycaemia, hyperglycaemia, time in range and GV.

Evaluation of the AGP output and guidelines for its interpretation have been published elsewhere.^{39 40}

Outcomes

Our primary outcome measure is the absolute difference in mean HbA1c at 12 months between the intervention and control arm.

Our secondary outcome measures are (a) per cent time in target (4–10 mmol/L) range, assessed via r-CGM device; and (b) diabetes-specific distress as measured by the Problem Areas in Diabetes (PAID) scale.⁴¹

Our hypotheses are that

1. The absolute difference in mean HbA1c at 12 months between the intervention and control arm will be $\geq 0.5\%$, favouring the intervention arm.
2. Glucose time in target (%) will favour the intervention arm.
3. No difference in diabetes-specific distress (mean PAID scores) will be observed at 12 months between intervention and control arm.
4. Cost effectiveness will favour the intervention arm.

Other r-CGM outcomes will include per cent time below target range (<4.0 mmol/L) and very low (<3.0 mmol/L) range (level 1 and level 2 hypoglycaemia⁴²) and per cent time in high (>10.0 mmol/L) and very high (>15.0 mmol/L) range; GV as reflected by SD and Mean Amplitude of Glucose Excursions; per cent of r-CGM trace available for 14 days. Other clinical measures

Table 2 Details and timing of data collection

| Measures | | Month | | | | |
|--|--|-------|----|----|----|----|
| | | 0 | 3 | 6 | 9 | 12 |
| Clinical | Rx, comorbidity | x | | | | x |
| | Behavioural change recommendations made; Rx changes prescribed | | x | x | x | x |
| Biometric | Weight, height | x | | | | x |
| Glycaemia | HbA1c | x | | x | | x |
| Other path | Lipids, creatinine, spot urine albumin-creatinine ratio | x | | | | x |
| r-CGM | AGP | x | x* | x* | x* | x |
| Psycho-social | ▶ Diabetes distress: Problem Areas in Diabetes scale ⁴¹ | x | | | | x |
| | ▶ Satisfaction with and user experience of glucose monitoring: Glucose Monitoring Experience Questionnaire ⁴⁹ | | | | | |
| | ▶ General Emotional Well-being: WHO (five) Well-being Index ⁵⁰ | | | | | |
| | ▶ Hypoglycaemia frequency and severity: selected items from the Hypoglycaemia Awareness Questionnaire ⁵¹ | | | | | |
| | ▶ Diabetes-specific quality of life: DAWN Impact of Diabetes Profile ⁵² | | | | | |
| | ▶ Health status: EuroQoL 5 Dimensions ⁵³ | | | | | |
| | ▶ Summary of Diabetes Self-care Activities ⁵⁴ | | | | | |
| ▶ Perceived involvement in Self-Care scale ⁵⁵ | | | | | | |

*Data collected for intervention arm only.

AGP, ambulatory glucose profile; r-CGM, retrospective continuous glucose monitoring.

include recording of the behavioural change recommendations made, medication changes prescribed, weight and height. Other psychological outcomes are detailed in [table 2](#).

Blinding

Participants in the intervention arm will be able to see their baseline r-CGM tracing as part of their baseline clinic assessment visit, while those randomised to the control arm will not have access to their baseline CGM tracing. The final 12-month tracing will be available to participants in both arms (following final data collection), enabling the GP and PN to use that as part of clinical management for all study participants.

Data collection, management and analysis

Collection of clinical, biometric and psychosocial data is summarised in [table 2](#).

Qualitative exploration of experience with and perceived impact of r-CGM and the collaborative care decision-making model will be explored at the end of the study in semistructured interviews with a sample of GPs/PNs (~N=10) and intervention participants (~N=20), with stratification based on participant characteristics and outcomes. We will explore usability and acceptability of the intervention, confidence in r-CGM, perceived impact of r-CGM (on glucose levels, diabetes management, quality of life), and perceived advantages and disadvantages of r-CGM and the collaborative care model. Interviews will be audio-recorded, transcribed and the data will be subjected to thematic analysis.

Health service utilisation will be obtained from relevant Victorian and Australian datasets. Participants have the option to also consent to provide a blood sample for use in an ancillary study of epigenetic markers associated with GV (see online supplementary appendix 2).

Power calculation, sample size and data analysis

Based on an individually RCT, stratified by practice, the sample size has 80% power to detect a difference in mean HbA1c of 5.5 mmol/mol (0.5%) with an SD of 14.2 (1.3%)⁴³ and an alpha of 0.05. The required number of participants in each arm is n=108, a total of n=216. Assuming a 20% attrition rate, this inflates to n=270 (n=135 in each arm). Allowing for 10% clinic attrition and assuming six participants per clinic, we are thus aiming to recruit n=300 participants (n=150 in each arm).

Clinic, GP and patient characteristics at baseline will be summarised for each study group and assessed for imbalance. Mean HbA1c levels at baseline and 12 months will be plotted for each study arm.

A linear mixed-effects model (ie, with both fixed effect for treatment and time and random effect for clinic and repeated patient HbA1c measurements) will be used to estimate the group difference in HbA1c at 12 months using restricted maximum likelihood estimation. The model will include the HbA1c at baseline, 6 months and 12 months and be adjusted by age and history of hypoglycaemia should these be imbalanced between the arms at baseline. A secondary analysis will examine whether the intervention effect differs between those with and without a history of severe hypoglycaemia. The same approach

will be used to determine whether the intervention effect varies for those with a general HbA1c target compared with those with a personalised HbA1c target.

Analysis will be based on an intention-to-treat approach. Mixed models assume any missing data are missing at random. Hence, sensitivity analyses will be conducted to assess the robustness of this assumption. A full statistical analysis plan for the trial will be published separately.

We will use the United Kingdom Prospective Diabetes outcomes simulation model (with updated Australian equations where possible) to perform economic evaluation.⁴⁴ The impact of diabetes on morbidity, mortality, health status and healthcare costs will be estimated for each arm during the trial period and beyond using a model based on risk factors and complications. Health status impacts for the two arms will be incorporated using EQ5D weights to allow estimation of cost utility. The model allows extrapolation from the trial outcomes to downstream events and complications, including estimation of the long-term impact of changes in disease management. Costs of monitoring and education will be sourced from trial administrative databases. In addition, costs associated with the health states (eg, stroke, heart disease) will be obtained from relevant Victorian and Australian data sets. The results of the economic modelling will be presented as incremental cost per quality-adjusted life-year (QALY) gained at trial conclusion and full life expectancy for the r-CGM arm relative to the control arm.

Monitoring

We will collect data on the fidelity of the intervention (if GPs have undertaken the training in r-CGM use and interpretation and adherence to the 3-monthly visits through collection of Clinic Assessment Visit (CAV) forms, which also ask if any technical problems have been encountered in relation to the sensor, including local skin reactions). Adverse events may also be reported at CAVs and are collected at follow-up data collection using standard operating procedures. A safety monitoring committee consisting of one GP, one RN-CDE and one endocrinologist will be appointed to review significant adverse events, which includes any episodes of severe hypoglycaemia, and their duration, treatment and outcome.

Patient and public involvement

Patients and/or public were not involved in the development of the research question and outcome or the design of this study.

Ethics and dissemination

Ethics approval has been obtained from the University of Melbourne Health Sciences Human Ethics Sub Committee (Ethics ID 1647151.1). All participating health professionals and people with T2D will sign a consent form prior to participating. We will disseminate the results in peer-reviewed journals, presentations at scientific meetings and will also provide a plain language

summary to study participants. Data will be retained in secure storage at the University of Melbourne in accordance with National Health and Medical Research Council (NHMRC) Guidelines.

DISCUSSION

Our proposal tackles an important clinical problem with significant health and cost implications for the 1.1 million Australians with T2D in primary care, half of whom have glycaemic levels above recommended target range. While we chose an evidence-based, clinically meaningful primary outcome (HbA1c), our trial is based on the premise that novel glucose monitoring technologies provide a potential tool for GPs and people with T2D to visualise blood glucose patterns clearly, enabling them to make evidence-based and personalised treatment choices and plans to achieve optimal glycaemic targets. Below we discuss the key innovative features of our study design.

We are conducting a pragmatic, individually RCT as it will produce robust data about the true effect of our intervention. We will train all GPs to use and interpret the results of r-CGM, while only half of their participating patients will be using the technology as part of clinical care. The amount of glucose data available to GPs in managing intervention and control group participants will thus differ significantly. GPs' confidence and clinical skills in T2D management may be enhanced (in relation to treatment intensification, built through seeing the glucose profiles of people with T2D and the effect of medication and lifestyle changes in intervention participants). However, we do not believe significant contamination between arms is likely to occur as the application of any new skills in the control arm will be limited by lack of access to detailed, personalised glucose profiles, which will not be available for control group participants. The 3-monthly review prompts and the 1 hour Diabetes Educator session will be standardised exposures across both arms, enabling us to isolate the effect of the r-CGM device used in the intervention group. We chose usual care as our comparator group as s-SMBG is not currently routine practice in Australia and does not feature in current NHMRC or Royal Australian College of General Practitioners (RACGP) guidelines.⁴⁵

Personalised use of self-monitoring devices is a burgeoning and rapidly changing field. Automated and seamless data collection and presentation is a critical factor in the usability of such technology. We chose a retrospective, professionally held CGM technology for several reasons. This first is that people with T2D have relatively stable and simple glucose profiles on a day-to-day basis.⁴⁶ This contrasts with people with T1D who have more unpredictable glucose profiles with more GV. Thus, people with T1D need real-time glucose data while people with T2D can learn much about their own glucose profiles and the effects of medication

and behaviours from retrospective data, and then use that to effect self-management changes. Based on our experience and understanding of the general practice setting, we expect that the clinical use of r-CGM would fit well with existing patterns of clinical practice. Insertion of a sensor is done relatively quickly by either the GP or PN. At a scheduled follow-up appointment, the sensor data can be uploaded easily and viewed in a regular consultation with a GP, and the report format enables easy visualisation and collaborative discussion of tangible self-management changes between the GP and the person with T2D.

There are now several r-CGM devices available in the Australian market. This study is investigator-initiated, funded by the Australian National Health and Medical Research Council, and the investigator group has no commercial interest with the manufacturer of these devices. However, we structured our study around the use of an automated device requiring no finger-prick calibration as we believe this is the most likely form and direction that the technology will take in the future, with minimal burden on the person with T2D addressing a key barrier to S-SMBG levels.

Our study embeds r-CGM technology within a supportive and collaborative educational framework for the GP and PN and the person with T2D. r-CGM needs to be integrated within an educational intervention that promotes and supports patient engagement with possible behavioural changes and treatment adjustments.

Hypoglycaemia, and in particular nocturnal hypoglycaemia, in people with T2D is significant but commonly under-reported in RCTs (especially in those on insulin)⁴⁷ and elsewhere.⁴⁸ As a pragmatic real-world study, our trial also offers a unique opportunity to gather robust data on the prevalence of hypoglycaemia among a primary care T2D population.

Limitations of our study are that no independent monitoring has been performed and that serious adverse events were not structurally assessed (ie, reporting was dependent on the clinicians at the participating practices).

Our study will provide important evidence of the effectiveness of new r-CGM technologies as they inevitably enter the community, enabling rational clinical and health policy decisions, potentially shaping T2D clinical practice in Australia and around the world, with impact on health and healthcare costs.

Author affiliations

¹Department of General Practice, University of Melbourne, Carlton, Victoria, Australia

²Department of Medicine, St Vincent's Hospital, University of Melbourne, Melbourne, Australia

³School of Psychology, Deakin University, Geelong, Victoria, Australia

⁴The Australian Centre for Behavioural Research in Diabetes, Diabetes Victoria, Melbourne, Victoria, Australia

⁵Latrobe University, Wodonga, Victoria, Australia

⁶Diabetes Research Centre, University of Leicester, Leicester General Hospital, Leicester, UK

⁷University of Melbourne, Melbourne, Australia

⁸NHMRC Clinical Trials Centre, The University of Sydney, NSW 2006, Australia

⁹Centre of Cardiovascular Research and Education in Therapeutics, Monash University, Melbourne, Victoria, Australia

¹⁰University of Melbourne, Melbourne, Australia

¹¹Lee Kong Chian School of Medicine, Nanyang Technological University, Singapore

Acknowledgements KK acknowledges support from the National Institute for Health Research Collaboration for Leadership in Applied Health Research and Care, East Midlands (NIHR CLAHRC, EM), and the NIHR Leicester Biomedical Research Centre.

Contributors JF, DNO, N, JS, IB, J-AM-N, KK, KD and JB developed the study concept and aims and initiated the project. ST, KdLR, LG, JLB, EH-T, JC, RA, MK, MC, AJJ, DL, PC and JB assisted in further development of the protocol. JF was responsible for drafting the manuscript. KdLR, ST and LG implemented the protocol and oversaw collection of the data. All authors contributed to the final manuscript.

Funding This work was supported by the National Health and Medical Research Council Project Grant (ID APP1104241). Additional funding has been provided by Sanofi Australia. In-kind support has been provided by Abbott Diabetes Care, which has provided the Libre Pro reader devices, sensors and software.

Disclaimer The funding body and industry partners have had no involvement in the design of the study and will have no role in the collection, analysis and interpretation of data or in writing any manuscripts describing the study outcomes. Study sponsor and funders have had no role in study design or data analysis plans.

Competing interests JF has received unrestricted educational grants for research support from Roche, Sanofi and Medtronic; JS is a member of the Accu-Check Advisory Board (Roche Diabetes Care) and also served on the advisory boards of Janssen and Medtronic. Her research group has received unrestricted educational grants from AstraZeneca, Medtronic and Sanofi Diabetes; sponsorship to attend educational meetings from Medtronic, Roche Diabetes Care, and Sanofi Diabetes; consultancy income and/or speaker fees from Abbott Diabetes Care, AstraZeneca, Roche Diagnostics Australia and Sanofi Diabetes; DON is on advisory boards to Abbott Diabetes Care, and Novo-Nordisk. DON, DL and JMN have had various financial relationships with pharmaceutical industries outside the submitted work including consultancies, grants, lectures, educational activities and travel. IB has received investigator initiated grant from Medtronic and Sanofi Diabetes. EHT has undertaken research funded by an unrestricted educational grant from Abbott Diabetes Care to ACBRD and has served on an AstraZeneca advisory board. JLB has received consultancy income (paid to the ACBRD) from Sanofi ANZ and Roche Diagnostics, and travel funds from AstraZeneca, and has served on a Sanofi ANZ advisory board. KK has acted as a consultant, speaker or received grants for research from Astra Zeneca, Novartis, Novo Nordisk, Sanofi-Aventis, Lilly, Merck Sharp & Dohme, Janssen, Boehringer Ingelheim and Roche. JF was supported by a National Health and Medical Research Council Career Development Fellowship and then a Translating Research into Practice Fellowship. JS, JLB and EH-T are supported by core funding to the Australian Centre for Behavioural Research in Diabetes from Diabetes Victoria and Deakin University.

Patient consent Obtained.

Ethics approval University of Melbourne Human Ethics Sub-Committee.

Provenance and peer review Not commissioned; externally peer reviewed.

Open access This is an open access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited, appropriate credit is given, any changes made indicated, and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>.

REFERENCES

- Zimmet PZ, Magliano DJ, Herman WH, *et al.* Diabetes: a 21st century challenge. *Lancet Diabetes Endocrinol* 2014;2:56–64.
- Holman RR, Paul SK, Bethel MA, *et al.* 10-year follow-up of intensive glucose control in type 2 diabetes. *N Engl J Med* 2008;359:1577–89.
- Williamson M, Gillies M, Merrifield A, *et al.* Snapshot of type 2 diabetes care in general practice: first results from MedicinesInsight. Canberra: Primary Health Care Research Conference, 2014.
- Edelman SV, Polonsky WH. Type 2 diabetes in the real world: the elusive nature of glycemic control. *Diabetes Care* 2017;40:1425–32.

5. Gaede P, Vedel P, Larsen N, *et al.* Multifactorial intervention and cardiovascular disease in patients with type 2 diabetes. *N Engl J Med* 2003;348:383–93.
6. Sonne DP, Hemmingsen B. Standards of Medical Care in Diabetes-2017. *Diabetes Care* 2017;40(Suppl. 1):S1–S135. Diabetes Care 2017, 40(7):E92–E93.
7. Gunton JE, Cheung NW, Davis TM, *et al.* A new blood glucose management algorithm for type 2 diabetes: a position statement of the Australian Diabetes Society. *Med J Aust* 2014;201:650–3.
8. Rydén L, Grant PJ, Anker SD, *et al.* ESC Guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD: the Task Force on diabetes, pre-diabetes, and cardiovascular diseases of the European Society of Cardiology (ESC) and developed in collaboration with the European Association for the Study of Diabetes (EASD). *Eur Heart J* 2013;34:3035–87.
9. Zafar A, Stone MA, Davies MJ, *et al.* Acknowledging and allocating responsibility for clinical inertia in the management of Type 2 diabetes in primary care: a qualitative study. *Diabet Med* 2015;32:407–13.
10. Parchman ML, Pugh JA, Romero RL, *et al.* Competing demands or clinical inertia: the case of elevated glycosylated hemoglobin. *Ann Fam Med* 2007;5:196–201.
11. Holmes-Truscott E, Blackberry I, O'Neal DN, *et al.* Willingness to initiate insulin among adults with type 2 diabetes in Australian primary care: Results from the Stepping Up Study. *Diabetes Res Clin Pract* 2016;114:126–35.
12. McGuire H, Longson D, Adler A, *et al.* Management of type 2 diabetes in adults: summary of updated NICE guidance. *BMJ* 2016;353:i1575.
13. American Diabetes Association. Standards of Medical Care in Diabetes-2016 Abridged for Primary Care Providers. *Clin Diabetes* 2016;34:3–21.
14. Farmer AJ, Perera R, Ward A, *et al.* Meta-analysis of individual patient data in randomised trials of self monitoring of blood glucose in people with non-insulin treated type 2 diabetes. *BMJ* 2012;344:e486.
15. Malanda UL, Welschen LM, Riphagen II, *et al.* Self-monitoring of blood glucose in patients with type 2 diabetes mellitus who are not using insulin. *Cochrane Database Syst Rev* 2012;1:CD005060.
16. Speight J, Browne JL, Furler JS. Testing times! Choosing Wisely when it comes to monitoring type 2 diabetes. *Med J Aust* 2015;203:354–6.
17. Polonsky WH, Jelsovsky Z, Panzera S, *et al.* Primary care physicians identify and act upon glycemic abnormalities found in structured, episodic blood glucose monitoring data from non-insulin-treated type 2 diabetes. *Diabetes Technol Ther* 2009;11:283–91.
18. Polonsky WH, Fisher L, Schikman CH, *et al.* Structured self-monitoring of blood glucose significantly reduces A1C levels in poorly controlled, noninsulin-treated type 2 diabetes: results from the Structured Testing Program study. *Diabetes Care* 2011;34:262–7.
19. Fisher L, Polonsky WH, Parkin CG, *et al.* The impact of structured blood glucose testing on attitudes toward self-management among poorly controlled, insulin-naïve patients with type 2 diabetes. *Diabetes Res Clin Pract* 2012;96:149–55.
20. Barendse S, Singh H, Frier BM, *et al.* The impact of hypoglycaemia on quality of life and related patient-reported outcomes in Type 2 diabetes: a narrative review. *Diabet Med* 2012;29:293–302.
21. Heller S, Amiel SA, Khunti K. International Hypoglycaemia Study Group. Hypoglycaemia, a global cause for concern. *Diabetes Res Clin Pract* 2015;110:229–32.
22. Nalysnyk L, Hernandez-Medina M, Krishnarajah G. Glycaemic variability and complications in patients with diabetes mellitus: evidence from a systematic review of the literature. *Diabetes Obes Metab* 2010;12:288–98.
23. Pickup JC. Banting Memorial Lecture 2014* Technology and diabetes care: appropriate and personalized. *Diabet Med* 2015;32:3–13.
24. Haak T, Hanaire H, Ajan R, *et al.* Use of Flash Glucose-Sensing Technology for 12 months as a Replacement for Blood Glucose Monitoring in Insulin-treated Type 2 Diabetes. *Diabetes Ther* 2017;8:573–86.
25. Beck RW, Riddlesworth TD, Ruedy K, *et al.* Continuous Glucose Monitoring Versus Usual Care in Patients With Type 2 Diabetes Receiving Multiple Daily Insulin Injections: A Randomized Trial. *Ann Intern Med* 2017;167:365.
26. Kesavadev J, Vigersky R, Shin J, *et al.* Assessing the Therapeutic Utility of Professional Continuous Glucose Monitoring in Type 2 Diabetes Across Various Therapies: A Retrospective Evaluation. *Adv Ther* 2017;34:1918–27.
27. Vigersky R, Shrivastav M. Role of continuous glucose monitoring for type 2 in diabetes management and research. *J Diabetes Complications* 2017;31:280–7.
28. Blackberry ID, Furler JS, Ginnivan LE, *et al.* An exploratory trial of basal and prandial insulin initiation and titration for type 2 diabetes in primary care with adjunct retrospective continuous glucose monitoring: INITIATION study. *Diabetes Res Clin Pract* 2014;106:247–55.
29. Mohan V, Jain S, Kesavadev J, *et al.* Use of Retrospective Continuous Glucose Monitoring for Optimizing Management of Type 2 Diabetes in India. *J Assoc Physicians India* 2016;64:16–21.
30. Barnard KD, Oliver N. Technological advancement in the treatment of diabetes-ignoring psychosocial impact at our peril. *Diabetes Technol Ther* 2015;17:149–51.
31. Gonder-Frederick LA, Shepard JA, Grabman JH, *et al.* Technology, and Diabetes Management. *American Psychologist* 2016;71:577–89.
32. Abu Hassan H, Tohid H, Mohd Amin R, *et al.* Factors influencing insulin acceptance among type 2 diabetes mellitus patients in a primary care clinic: a qualitative exploration. *BMC Fam Pract* 2013;14:164.
33. Zwarenstein M, Treweek S, Gagnier JJ, *et al.* Improving the reporting of pragmatic trials: an extension of the CONSORT statement. *BMJ* 2008;337:a2390.
34. Boutron I, Moher D, Altman DG, *et al.* Methods and Processes of the CONSORT Group: Example of an Extension for Trials Assessing Nonpharmacologic Treatments. *Ann Intern Med* 2008;148:W-60–W66.
35. Cheung NW, Conn JJ, d'Emden MC, *et al.* Position statement of the Australian Diabetes Society: individualisation of glycated haemoglobin targets for adults with diabetes mellitus. *Med J Aust* 2009;191:339–44.
36. Harris PA, Taylor R, Thielke R, *et al.* Research electronic data capture (REDCap)—a metadata-driven methodology and workflow process for providing translational research informatics support. *J Biomed Inform* 2009;42:377–81.
37. Polonsky WH, Fisher L, Schikman CH, *et al.* A structured self-monitoring of blood glucose approach in type 2 diabetes encourages more frequent, intensive, and effective physician interventions: results from the STeP study. *Diabetes Technol Ther* 2011;13:797–802.
38. Speight J, Browne JL, Furler J. Challenging evidence and assumptions: is there a role for self-monitoring of blood glucose in people with type 2 diabetes not using insulin? *Curr Med Res Opin* 2013;29:161–8.
39. Matthaei S. Assessing the value of the Ambulatory Glucose Profile in clinical practice. *British Journal of Diabetes* 2014;14:148–52.
40. Matthaei S, DeAlaiz RA, Bosi E, *et al.* Consensus recommendations for the use of Ambulatory Glucose Profile in clinical practice. *British Journal of Diabetes* 2014;14:153–7.
41. Polonsky WH, Anderson BJ, Lohrer PA, *et al.* Assessment of diabetes-related distress. *Diabetes Care* 1995;18:754–760.
42. International Hypoglycaemia Study Group. Glucose Concentrations of Less Than 3.0 mmol/L (54 mg/dL) Should Be Reported in Clinical Trials: A Joint Position Statement of the American Diabetes Association and the European Association for the Study of Diabetes. *Diabetes Care* 2017;40:155.
43. Furler J, O'Neal D, Speight J, *et al.* Supporting insulin initiation in type 2 diabetes in primary care: results of the Stepping Up pragmatic cluster randomised controlled clinical trial. *BMJ* 2017;356:j783.
44. Clarke PM, Gray AM, Briggs A, *et al.* A model to estimate the lifetime health outcomes of patients with type 2 diabetes: the United Kingdom Prospective Diabetes Study (UKPDS) Outcomes Model (UKPDS no. 68). *Diabetologia* 2004;47:1747–59.
45. Colagiuri R, Giris S, Eigenmann C, *et al.* R. G: National evidence-based guidelines for patient education in type II diabetes. Canberra: Diabetes Australia and NHMRC, 2009.
46. Manski-Nankervis J, Yates CJ, Blackberry I, *et al.* Impact of insulin initiation on glycaemic variability and glucose profiles in a primary healthcare Type 2 diabetes cohort: analysis of continuous glucose monitoring data from the INITIATION study. *Diabet Med* 2016;33:803–11.
47. Elliott L, Fidler C, Ditchfield A, *et al.* Hypoglycemia Event Rates: A Comparison Between Real-World Data and Randomized Controlled Trial Populations in Insulin-Treated Diabetes. *Diabetes Ther* 2016;7:45–60.
48. Khunti K, Alsifri S, Aronson R, *et al.* Rates and predictors of hypoglycaemia in 27 585 people from 24 countries with insulin-treated type 1 and type 2 diabetes: the global HAT study. *Diabetes Obes Metab* 2016;18:907–15.
49. Speight J, Holmes-Truscott E, Little S. *Psychometric Validation of the Novel Glucose Monitoring Experiences Questionnaire (GME-Q) among Adults with Type 1 Diabetes*. New Orleans: 76th Scientific Sessions of the American Diabetes Association, 2016.



50. World Health Organization: Regional Office for Europe. *Well-Being measures in primary health care: The DepCare Project. In. Consensus meeting*. Stockholm: World Health Organization: Regional Office for Europe, 1998.
51. Speight J, Barendse SM, Singh H, *et al*. Characterizing problematic hypoglycaemia: iterative design and preliminary psychometric validation of the Hypoglycaemia Awareness Questionnaire (HypoA-Q). *Diabet Med* 2016;33:376–85.
52. Nicolucci A, Kovacs Burns K, Holt RI, *et al*. Diabetes Attitudes, Wishes and Needs second study (DAWN2™): cross-national benchmarking of diabetes-related psychosocial outcomes for people with diabetes. *Diabet Med* 2013;30:767–77.
53. EuroQol Group. EuroQol--a new facility for the measurement of health-related quality of life. *Health Policy* 1990;16:199–208.
54. Toobert DJ, Hampson SE, Glasgow RE. The summary of diabetes self-care activities measure: results from 7 studies and a revised scale. *Diabetes Care* 2000;23:943–50.
55. Lerman CE, Brody DS, Caputo GC, *et al*. Patients' Perceived Involvement in Care Scale: relationship to attitudes about illness and medical care. *J Gen Intern Med* 1990;5:29–33.