1. TITLE

A systematic review of psychological interventions to improve motivation for self-management in people with type 1 and type 2 diabetes

1.1 Amendment history

The following amendments were made to version 1.2 of the protocol in response to reviewers' comments.

In the methods section we describe in more detail how data from a previous meta-analysis would be combined with the current systematic review, please see section 5.7.ii. We also clarified that we will limit the individual participant data meta-analysis to work published since the 2003 systematic review, please see section 5.7.iii.

We describe the data we would be using for the economic analysis for the individual patient simulation models and how we would address the issue of short term utilities was not addressed in the original protocol. One is general improvements in health and the other is the utility values associated with diabetic complications (section 5.7.vii).

We provided additional detail as to how we would ensure that potential practice recommendations from the systematic review are adopted by health professionals, in section 6.1 dissemination plan.

We increased the level of patient public involvement (PPI) by establishing a local membership team and national representation via the NHS England diabetes Clinical Reference Groups. Patients will be asked for their views on the research to date/review findings and how the findings should be disseminated and translated (see section 9.0).

The following amendment s were made to version 1.3 of the protocol.

We were more explicit in the exclusion criteria and now say that patients that have other medical conditions will be excluded unless the data on patients with diabetes have been summarised and extractable as a subgroup, or separate analysis can be provided by the author (section 5.1.ii).

We updated our definition of a psychological intervention (section 5.1.ii). We define an intervention as psychological if they include the following: i) had a reliance on communication, using a therapeutic alliance between patient and the therapist; ii) intervention was facilitated by psychologists, psychotherapists, and therapists in training, or facilitated by persons trained/supervised by a clinical psychologist or therapist; iii) the intervention was based on a psychological model; iv) the intervention aimed to improve outcome changes in emotional, cognitive or behavioural functioning including adherence. If these criteria were unclear and the intervention could not clearly be described as psychological, then authors were contacted for more information. If this criteria is unclear from publication, then authors will be contacted for more information to determine eligibility.

We included 'diabetes education' as a comparator (section 5.1.iv).

We searched international conference abstracts from 2012-current.We additionally searched Clinicaltrials.gov for grey literature (section 5.2).

2. SUMMARY OF RESEARCH

Self-management is the cornerstone of diabetes management yet the majority of patients struggle to achieve national targets for effective glycaemic control. Psychological factors such as depression, eating and weight concerns, diabetes specific fears and worries, acceptance of the diagnosis, coping, health beliefs, family distress and stigma, can reduce the motivation to self-manage. The last systematic reviews of randomised controlled trials (from 1966 to 2003) suggest that motivation is potentially modifiable using brief psychological interventions to address these psychological factors but the quality of most studies had limited validity. In the past decade the number of intervention studies has grown significantly. With the epidemic of type 2 diabetes and the rise in the incidence of type 1 diabetes, increasing awareness of the inequity of mental health services compared to physical health services, the rising costs of new anti-diabetes medications and medical devices, there is a need to develop and evaluate the most effective and cost-effective psychological interventions that optimise diabetes control. We propose to conduct a systematic review and meta-analysis of the effectiveness and cost-effectiveness of randomised and non-randomised controlled trials testing whether brief psychological interventions are effective in improving measures of self-management, glycaemic control and quality of life. The protocol will be based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines. We will stratify by type of diabetes, and for type 1 diabetes by children versus adults. We will search MEDLINE, PsychINFO, EMBASE, Cochrane Controlled Trials Database (since 2003-current), Web of Science and the grey literature for eligible studies. Using an *a priori* standardised format, we will extract qualitative and quantitative data that describe the clinical sample; the potential active ingredients such as theoretical framework, manual, behaviour change techniques, frequency and duration of sessions, format of delivery (face to face, telephone or e-therapy), group versus individual; unit costs; assessment of bias using the Cochrane Handbook checklist; and measures of self-management or behaviour change, glycaemic control and quality of life. We will conduct meta-analyses, individual participant and network meta-analyses, sensitivity and subgroup analyses and statistical assessment of bias. We propose to undertake a cost-effectiveness analysis of the psychological interventions via four components of health economic evaluation related work, namely review of the cost effectiveness literature, costing of the interventions, modelling of cost effectiveness and Health Economic Decision Modelling Analysis. We will compare our findings with previous reviews to identify any cohort effects or new developments in theory, policy and methodologies. Our findings will inform commissioners developing diabetes pathways and recommendations for primary research.

3. BACKGROUND AND RATIONALE

3.1 Natural history of diabetes mellitus

Diabetes mellitus is characterised by chronic hyperglycaemia which leads to microvascular and microvascular complications. The epidemiology and natural history of the two most common types, type 1 diabetes (T1DM) and type 2 diabetes (T2DM) are different and this is relevant because they have different profiles (but not mutually exclusive) of psychological factors that might interfere with self-management. T1DM represents 10% of diabetes cases, there is (near) absolute deficiency of insulin secondary to autoimmune destruction of β islet cells. Over 50% of T1DM presents in childhood or early adult life and patients must inject insulin to survive. T2DM represents 90% of all cases, there is progressive peripheral insulin resistance and relative insulin deficiency related to obesity, physical inactivity and increasing age, with the majority of cases presenting in mid-life (mid-50s for people of African-Caribbean, Asian or Latino ethnicity and mid-60s for people of white ethnicity). Treatment is initially with intensive lifestyle modification, followed by adding oral antidiabetes medication and with many people becoming insulin requiring after 10 years post diabetes (1). While glycaemic control is

important, control of other cardiovascular risk factors such as lipids and blood pressure is critically important in reducing the high risk of macrovascular disease (2, 3).

3.2 The construct of self-management

The management of diabetes requires patients to make changes to their lifestyles and take on new roles, more so than almost any other condition. For optimal diabetes control, people with diabetes need to self-manage their weight and diet, physical activity, oral medication, self-monitor their blood glucose (SMBG), titrate and inject insulin doses (either as multiple daily doses or via continuous subcutaneous insulin infusions) and increasingly incretin-based therapies. The ability to effectively self-manage is considered a fundamental skill for optimising glycaemic control and is enshrined in national guidance (2, 3). Diabetes pathways now include delivery of the necessary knowledge and practical skills to self-manage via structured education programmes. These include Dose Adjusted for Normal Eating (DAFNE)(4) and Bournemouth Type 1 Intensive Education (BERTIE) for T1DM (5) and Diabetes Education and Self Management for Ongoing and Diagnosed Diabetes (DESMOND) (6) and XPERT for T2DM (7) which have been variously evaluated, with level 1 evidence that they are associated with short-term improvement in glycaemic control for T1DM (4, 5, 8) but less for T2DM (7, 9). There is wide variation in the availability of structured education programmes for diabetes and when available only a minority attend (10). National audits report that only around 27% of T1DM and 65% of T2DM achieve national quality targets for optimal glycaemic control (HbA1c 48 mmol/mol to 58 mmol/mol (2, 3, 11). Putting into practice skills gained from structured education programmes requires high levels of motivation and self-efficacy which are dependent on psychological factors. Some people benefit from structured education whereas others do not because they are not motivated or ready to make the changes, and patients often struggle to maintain effective self-management without ongoing professional support. This suggests that the effectiveness of delivering structured education programmes could be improved by addressing patient barriers to self-management.

3.3 Psychological barriers to self-management

Motivation is a psychological process that drives our reasons for our behaviours and in the context of diabetes, effective self-management. Motivation represents a person's willingness and belief (self-efficacy or confidence) to self-manage. Motivation can be affected by many factors. It is now universally recognised that people with diabetes also have high levels of psychological distress which can affect motivation and interfere with self-management.

While there is some debate as to how to classify the wide range of psychological problems that are common in diabetes, such as psychiatric disorders, lack of confidence, coping skills and health beliefs, the literature clearly describes several psychological constructs, namely depression, disordered eating and weight concerns, expressed emotions in families, diabetes-specific anxiety (such as fear of hypoglycaemia, of hyperglycaemia and of complications, adjustment and denial of diagnosis, shame and stigma and diabetes distress) which reduce motivation to adhere to diabetes self-care. Syntheses of epidemiological studies have reported pooled prevalence of depressive disorders using diagnostic interviews of around 10%, and of depressive symptoms is around 30%, both twice as common as in the general population (12-14). Depression is associated with reduced diabetes self-care (15), diabetes distress (16), suboptimal glycaemic control (17), diabetes complications (18) and premature mortality (19, 20). The prevalence of eating disorders is increased 2 fold, with nearly half of young women with T1DM reporting omitting insulin doses for fear of weight gain. Eating disorders are associated with up to 6-fold increased mortality in T1DM (21, 22). Diabetes distress, which has been defined as concerns relating to diabetes self-management, support, access to diabetes care and emotional burden of diabetes (23), has been proposed by some researchers to have a greater proximal effect on self-management than depression (16). It is thought that depression measures capture the negative emotional aspects of diabetes-specific distress although there is a strong correlation between the two. Cultural beliefs and values

contributing to the development of unhelpful health beliefs has been repeatedly recognised (24, 25) and are potentially modifiable targets in self-management.

3.4 Definition and classification of psychological treatments

Investigators have increasingly been examining whether, and which, psychological (sometimes also termed psychotherapeutic) treatments are most effective in improving motivation to self-management which mediates glycaemic control. Motivational or psychological interventions are distinct from other types of health technology such as education, medical devices, pharmacological agents and surgery. The fundamental principle underlying psychological treatments are that they utilise the psychotherapeutic (talking or communicating) relationship between the therapist and the patient to bring about change in emotional, cognitive and/or behavioural functioning. There is no consensus classification for the wide range of psychological treatments that may be applicable to increasing motivation in diabetes self management but broadly they can be categorised according to their theoretical framework as used by NHS choices (www.nhs.uk), current behaviour change taxonomies and other health agencies (26-28).

1. Psychoanalytical therapies: this utilises the therapeutic relationship to explore and resolve unconscious conflicts often arising from experiences and modelling in childhood that affect personality and interpersonal functioning into adult life. This tends to be an intensive and long-term therapy but brief psychodynamic models have been developed (29-31).

2. Cognitive behaviour therapy (CBT): this is a brief therapy (usually 6-20 sessions) that focuses on the here and now by identifying unhelpful thoughts and feelings linked to our actions (see figure 1 for a CBT formulation for diabetes). It aims to identify and challenge the underlying dysfunctional beliefs that maintain negative automatic thinking that occurs in certain situations, such as having to check one's blood glucose in public, using a broad range of techniques such as hypothesis testing, thought records, cognitive restructuring, Socratic questioning, behavioural tasks and skills training, problem solving, relaxation techniques, dialectical behaviour therapy. The evidence base for CBT in treating depression is extensive (32). There have been a growing number of intervention studies testing CBT or psychological techniques within the umbrella of CBT to improve self-management. In recent years, there has been an emergence of mindfulness or acceptance-commitment CBT which uses techniques derived from eastern philosophies and have been tested in diabetes(33).

3. Counselling is sometimes described as person-centred therapy and there are two main variations. Rogerian or humanistic therapy is an experiential non manualised and usually non focused therapy where ventilation of emotions is expected to lead to self-awareness and self-determination (34). Motivational interviewing is a counselling approach which focuses on behavior change. It is defined as a collaborative, goal-oriented style of communication with particular emphasis on the language of change (35). It is designed to strengthen personal motivation for, and commitment, to a specific goal by eliciting and exploring the person's own reasons for change using a non-judgmental, accepting and compassionate approach (36, 37). A motivational interviewing intervention moves through the following processes: engaging, focusing, evoking and planning. The core skills of motivational interviewing can by summarised by the acronym OARS: Open question; Affirmations; Reflections and Summaries. The appeal of MI is that it is very brief (1-4 sessions), and is effective for a range of lifestyle related behaviours and conditions including diabetes (38) by a range of health providers with a quality assurance competency framework.

4. Other psychotherapies and variations: interpersonal psychotherapy which was developed originally as a time limited (16 sessions) therapy for depression, it uses the connection between mood and interpersonal experiences to focus on grief, role dispute, role transition and interpersonal deficits (39). Cognitive analytical therapy combines psychoanalytical theory with CBT theory and has been tested in diabetes and is used in NHS diabetes clinics (40). Family or systemic therapies focuses on the principle

that family relationships operate as systems. For instance, sometimes the family member with diabetes may be singled out as the index problem, systemic therapy encourages everyone within the family to work together to fix problem rather than blaming each other (41).

There are other psychotherapies that use the creative process as the form of communication between the patient and the therapist, such as narrative writing (42), psychodrama (43) and art therapy (44). Increasingly the use of e-techniques to deliver psychological or motivational communications to support self-management such as text messaging and online programmes are being developed and evaluated (45, 46).

3.5 Current evidence for effectiveness of psychological treatments to improve glycaemic control

In the 1990s, there was a slow growth of intervention studies examining the effectiveness of psychological treatments to support self-management which led to a number of reviews some of which were not guided by standard systematic review methodologies (47-49) and the key findings were that many studies combined T1DM and T2DM; often the psychological active ingredients could not be distinguished from educational active ingredients; and they did not report standardised outcomes that could be pooled.

In a Cochrane Collaboration approved protocol, we conducted the first systematic review and meta-analysis of randomised controlled trials (RCT) of psychological treatments to improve glycaemic control separating T1DM and T2DM (50, 51). We found that there were significantly reduced quality for most RCTs such as lack of statistical power, selection bias, glycaemic control as a secondary outcome therefore prone to missing data, poorly described theoretical models underpinning the psychological treatment, limited information on the skills of the therapist and description of the intervention so that it was difficult to replicate the treatment. Overall there was some evidence that interventions using CBT-like techniques were more effective in improving glycaemic control. There were 29 studies eligible for the T1DM systematic review. In the 10 studies in children and adolescents with T1DM and with data for the meta-analysis, there was weak evidence that psychological treatments were effective (standardised pooled mean difference -0.35 (95% confidence interval -0.66 to -0.04)) equivalent to IFCC 6 mmol/mol absolute reduction in glycated haemoglobin. There was no evidence that psychological treatments were effective in 11 studies of adults with T1DM (pooled standardised mean difference was -0.17 (-0.45 to 0.10), equivalent to 3 mmol/mol absolute reduction in glycated haemoglobin). There were 25 T2DM studies eligible for inclusion but only 12 studies (n=522) had patients whose data could be pooled (pooled mean difference -0·32 (95% CI -0·57 to -0·07) equivalent to an absolute difference of in HbA1c of IFCC 8mmol/mol). These reviews met the Centre for Reviews and Dissemination (CRD) Database of Abstracts of Reviews of Effects (DARE) scientific quality criteria for a systematic review (52).

A later review in T2DM that synthesized the same studies found that general medical professionals were as effective in supporting self-care using psychological techniques (53). Since then the focus of systematic reviews in adults with T2DM has shifted to examine different modes of delivery such as computer-based/e-health interventions (54, 55), or techniques to support isolated self-management activities such as change in physical activity (56) or longer-term clinical outcomes, morbidity and mortality (57).

For children and adolescents with T1DM a similar picture has emerged with systematic reviews on family interventions (58), psycho-educational interventions (59, 60) and interventions incorporating physical activity (61). For adults with T1DM there have been no further systematic reviews of psychological treatments to support self-management, especially following structured education programmes.

In parallel but not mutually exclusive, as depression is so common, relatively easy to measure and is treatable, some researchers have focused solely on the treatment of depression in diabetes with the

primary aim of improving depression outcomes with the secondary aim that any improvement in glycaemic control would be mediated by improved self-management. There have now been several systematic reviews synthesizing this literature. They have consistently found that the depression in diabetes can be treated effectively with psychological, pharmacological interventions or as combined treatments, and increasingly as collaborative care (or stepped care or algorithm based) interventions but the pooled evidence shows that improvement in depression is not always associated with an improvement in glycaemic control (19, 62, 63).

3.6 Recent individual studies

Although there have been no updated systematic reviews of psychological interventions to support self-management and improve glycaemic control inT1DM since 2003 there has been a steady and promising growth in the publication of individual controlled studies. In a HTA funded multi-centre RCT (A Diabetes and Psychological Therapy (ADaPT) study), we found that nurse-led psychological treatments combining motivational interviewing and CBT was more effective (but not more cost-effective) than usual care in improving glycaemic control (reduction in HbA1c -5.5mmol/mol) in 340 people with T1DM and persistent suboptimal glycaemic control (64-66). Since then there have been numerous further RCTs of psychological interventions for adults with T1DM with sub-optimal diabetes control using group CBT demonstrating improvements in psychological and clinical outcomes (67-70). For instance, one of the most effective used 8 weekly sessions of guided self-determination group counselling delivered by nurses and demonstrated improvements in perceptions of self-efficacy, SMBG and HbA1c (mean difference 5 mmol/mol, $p<0.001$) compared with the usual care group (67).

In a scoping review we found more than 20 studies of psychological strategies to support motivation for self-management in children and adolescents with T1DM since the last review which ended in 2003 (51). Some of the most successful targeted the family and parents. An individual counselling 'personal trainer' programme (n=179) aimed to support young people to improve self-management by helping them with communicating their needs for support from family members (71) and the other behavioural family systems therapy specific to diabetes (n=189) concentrated on adherence to diabetes treatment and reducing family conflict to aid communication (72). The recent landmark UK multi-centre intervention (n=362), Child and Adolescent Structured Competencies Approach to Diabetes Education (CASCADE), which delivered motivational interviewing to support young people and their families with diabetes self-management led to improvements in family relationships and diabetes self-efficacy at 12 months of which the latter was sustained at 24 months but no improvement in glycaemic control (73).

In T2DM recent studies incorporating psychological therapy for motivation have focused on isolated self-management activities such as diet (74), exercise (75), weight management (76) and medication adherence (77, 78). These have typically employed counselling strategies, such as motivational interviewing therapy, to facilitate lifestyle change (76). The Look AHEAD (Action for Health in Diabetes) clinical trial investigated the long-term impact of a multi-factorial intensive lifestyle intervention incorporating motivational techniques for over 5,000 people with T2DM who were overweight. At 12 months follow-up there were significant improvements in weight, HbA1c and cardiovascular risk factors (74). Recently, novel approaches have been developed to improve motivation with self-management with regard to starting insulin treatment in T2DM. For example, an RCT of structured glucose self-monitoring training patients to use blood glucose meters compared with a monitoring group, led to earlier initiation of insulin in the glucose monitoring arm (78).

3.7 Economic evaluation

There have been only a handful of intervention studies that have included a cost effectiveness analysis and these suggest that psychological treatments as adjuncts to diabetes care may be either cost neutral or more expensive (66, 73) .

3.8 Summary

Psychological factors that interfere with self-management are potentially modifiable using psychological treatments. There has been insufficient economic analysis of the benefits of psychological treatments. In the past decade, there have also been advancements in the methodology of behaviour change such as NICE guidance on behaviour change (79) and an MRC framework for classifying behaviour change techniques for identifying and describing specific psychological techniques highly valuable for translation into clinical practice (80). There is also more awareness that brief psychological treatments are often effective in the short term but is also becoming recognised that some people with diabetes need long term support or repeated courses of psychological support. In the follow up of the ADaPT study, we found that after 2 years the effects of CBT and MI had disappeared (81). We propose to conduct a systematic review of updated of intervention studies.

4. AIMS AND OBJECTIVES

The overall aim is to conduct a systematic review and meta-analysis of controlled trials of brief psychological treatments to:

1. assess the effectiveness of psychological interventions which aim to improve motivation for patients with T1DM and T2DM so that they have improved i) diabetes self-management ii) glycaemic control, iii) other behaviour change and iv) health related quality of life.

2. examine the overall cost-effectiveness analysis of psychological treatments in diabetes and to model the potential predicted savings in reducing risk of diabetes complications long term.

3. assess the effectiveness of different types or techniques of psychological treatments for i) better self-management, ii) glycaemic control.

4. examine whether psychological treatments are effective in addressing in populations who experience health inequalities such as different ethnic groups, severe mental illness and social deprivation

5. to conduct subgroup analyses to identify clinical characteristics of patients who have better or worse diabetes self-management or glycaemic control eg by age, gender, complication status.

6. to describe the development of new psychological theories and techniques, and of any advancements in research methodologies such as quality assurance of fidelity of intervention delivery or characteristics of control groups.

7. to identify gaps in the literature in order to make recommendations for primary research

8. to summarise the data for translation into the NHS via Health Improvement Networks, Diabetes Strategic Networks, Diabetes UK and Clinical Commissioning Groups.

5. RESEARCH PLANS

We will use the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines (82) and register the systematic review on the PROSPERO database (International Prospective Register of Systematic Reviews)(83). Where possible we aim to match with the methods for the systematic reviews we conducted from inception of electronic databases to 2003, for the potential to pool data from an older cohort of studies with those from the last 10 years (50, 51). The advantage of this

approach is that intervention methodologies and psychological technologies have improved as have the number of studies in the preceding decade and therefore we will not be contaminating the modern review with methodological biases and limitations of under reporting of older studies, and yet still have the data of pre -2003 to compare to the reviews. We will make a list of the changes or differences between our previously completed protocol and this one. The study flow chart will be presented according to PRISMA guidance(82).

5.1 Eligibility for review

5.1.i Types of studies

Eligible studies will be stratified by randomisation status into a) those that are randomised controlled trials, published and unpublished and b) non-randomised controlled trials. N-of-1 trials and pre-post observational studies will be excluded as there is no control group. We will only use the first arm of crossover trials to minimise the biases of a carryover effect. Where there are multiple publications of the same study, we will include the publication which reported the primary outcome of interest (HbA1c), but if necessary extract data from other publications, such as intervention protocols. This will be important when searching for economic analyses.

5.1.ii Types of participant

We will separate the review by T1DM and T2DM as they are distinct clinical groups. As there are different historical and international cut offs for suboptimal glycaemic control and as change in glycaemic control is sometimes a secondary outcome, we will not have a pre-defined minimum HbA1c for inclusion into the review. We will include all ages along the lifespan but for T1DM we will stratify by children and adolescents (as defined by the study authors) versus adult studies (from age 18 years unless otherwise stated in the study). The diagnosis of diabetes should be based on standard consensus criteria valid at the beginning of the trial. Patients that have other medical conditions will be excluded unless the data on patients with diabetes have been summarised and extractable as a subgroup, or separate analysis can be provided by the author. Patients with pre-diabetes states or other types of diabetes such as impaired glucose tolerance or gestational diabetes will be excluded. We will not exclude studies which have not described whether patients have received structured education because many studies do not always report this information.

5.1.iii Types of interventions (health technologies being assessed)

We will include brief psychological interventions that are described by the study's authors as psychological and if they are based on established psychotherapeutic principles and techniques as described by NHS Choices (www.nhs.uk), Royal College of Psychiatrists (27) and National Institute for Clinical Excellence and Health (Guidance PH6) (79). We define an intervention as psychological if they include the following: i) had a reliance on communication, using a therapeutic alliance between patient and the therapist; ii) intervention was facilitated by psychologists, psychotherapists, and therapists in training, or facilitated by persons trained/supervised by a clinical psychologist or therapist; iii) the intervention was based on a psychological model; iv) the intervention aimed to improve outcome changes in emotional, cognitive or behavioural functioning including adherence. If these criteria were unclear and the intervention could not clearly be described as psychological, then authors were contacted for more information. If this criteria is unclear from publication, then authors will be contacted for more information to determine eligibility. The minimum and maximum number of sessions of a psychological treatment will be one and 50 respectively. There is huge variation of therapies we will classify them broadly under the following categories: psychoanalytical/psychodynamic, cognitive behaviour techniques; counselling (including motivational interviewing and mindfulness); family therapies; creative therapies (including narrative, art therapy, music therapy and psychodrama). We will include

collaborative care i.e. a psychological intervention in combination with psychotropic or antidepressants. Typically brief interventions are estimated at around 20 sessions but we want to identify studies that have also addressed maintenance of self-management as diabetes is a chronic condition and there is a risk of relapse. Studies that used self-help (unless guided by a therapist) will be excluded.

5.1.iv Types of comparator

We will consider a control group defined as:

i) usual diabetes care: this will depend on the local pathways for diabetes care and whether they have been standardised for the study.

ii) usual care while on a waiting list: in some settings, eg depression, it may be unethical to deny effective treatments.

iii) attention control: a controversial criticism of psychological intervention studies is that the active ingredient is the extra time that a therapist spends with the patient rather than any specific techniques that brings about behaviour change.

iii) a less intense psychological treatment.

iv) diabetes education

The contents of the control intervention will be extracted in the same standardised protocol as for the intervention.

5.1.iv Type of outcomes

The main outcome will be any change in glycaemic control. If it is possible to measure the duration during which the change was maintained, then we will use this data in the economic modelling. The secondary outcomes will be i) changes in self-management activities as the main behaviour changes, such as SMBG, self-examination, diet, physical activity, oral anti-diabetes mediation, uptake of insulin therapy, increased clinic attendance ii) change in psychological functioning such as depressive symptoms, diabetes distress iii) economic outcomes using unit costs iv) adverse effects such as incidence of severe hypoglycaemia, diabetic ketoacidosis, diabetes complications.

5.2 Information sources

We will conduct an all language search from the following databases from February 2003 to current: identified trials in MEDLINE (since 2003 to current), CINAHL (since 2003 to current), *The Cochrane Library*, (current issue), PsycINFO (since 2003 to current), and EMBASE (since 2003 to current), Cochrane Controlled Trials Database (since 2003-current), Web of Science (since 2003-current) and Dissertation Abstracts International (since 2003 to current). Searches will be combined with the Cochrane Collaboration optimal search strategy for the identification of RCTs for each database adapting and updating the search strategy we used previously (50, 51). We will also carry out searches using selected MeSH and free text terms using keywords that are not in the search strategy on each database eg motivational interviewing, collaborative care, economic evaluation.

Abstracts of four international diabetes conferences will be searched from 2012 to current from Diabetes UK, American Diabetes Association, European Association for the Study of Diabetes, International Federation of Diabetes for reports of any trials using psychological therapies. The reference lists of included studies and reviews were searched for additional studies. Lead and senior authors of each included trial and experts in this subject will be contacted for patient level data and any additional

qualitative and quantitative data on unpublished and published trials. Clinicaltrials.gov will be searched for "active, not recruiting" with an estimated completion date of 2016, authors of any relevant papers identified will be contacted for full text paper availability.

5.3 Search Strategy

The following search terms will be used for MEDLINE and adapted for each database: "psychological therapies" and "mood disorders" and "diabetes distress" according to the Cochrane Collaboration Depression, Anxiety and Depression Group search strategy; "diabetes mellitus" and "clinical trials" according to the Cochrane Collaboration Metabolic and Endocrine Disorder Group generic diabetes search strategy and self-management including adherence, diet, physical activity, insulin therapy. Where existing search strategies do not exist, we will develop and pilot a version for this review.

We will search for cost-effectiveness evidence using standard search techniques and Scottish Intercollegiate Guidelines Network filters on databases for cost-effectiveness evidence (84). Although our decision problem is limited to the UK, we will search for international cost-effectiveness literature to ensure we examine any useful methodological developments for assessing these interventions as well as understanding how other researchers have found evidence for different parameters that will be important in the health economic models. The search will cover (separately) both T1DM and T2DM and the exact specification of interventions and of years for this search will be determined after the effectiveness evidence searches have been completed.

5.4 Study records

5.4.i Data Management

The abstracts will be reviewed online to reduce carbon load and organise information. We will establish a project management committee. Eligible studies will be filed by type of diabetes and then by year of publication. An excel spreadsheet will be used to manage records and data. Individual patient data will be requested as anonymised only and only if there is ethics committee approval. Investigators who contribute to individual data will be invited to be part of the writing group. The PI (who has led 7 systematic reviews and project managed two NIHR funded clinical trials) will develop the Standard Operating Procedures (SOP) to include *a priori* rules for standardising coding of data where ambiguities exist eg describing motivational interviewing as CBT.

5.4.ii Selection process

For the first stage, the abstracts of studies identified by the electronic searches will be independently inspected by two researchers (the PI and the research worker) and inter rater reliability for selection into the review will be calculated using Cohen's Kappa (85). At this stage, if the study is in a foreign language, we will only review abstracts that are also written in English as well as in that language. We will select abstracts that describe a controlled trial, a psychological or behavioural intervention, in patients with T1DM or T2DM. We will not include glycaemic control or self-management as a criterion for selection in abstracts because this may not be a primary outcome for some studies. In case of ambiguity or differences between raters, the abstract will be included into the second stage.

In the second stage, the two researchers will independently extract data from each full copy of the abstracts selected for further review. At this stage, we will include articles in foreign languages which will be translated by native speaking psychiatrists, psychologists, and if not available, medical interpreters. The value of this strategy is that it may help address health inequalities by identifying different cultural approaches to supporting self-management which could be translated to the UK's multicultural and ethnically diverse population with diabetes.

Differences over inclusion of studies for eligibility into the review will be resolved by consensus and discussion with third researcher (co-investigator KI).

In the third stage, the eligible study will be examined for adequate data, for pooling into the meta-analysis including sample size for each arm of the study, measure of the mean or median and its variance or spread or mean differences for each outcome.

5.4.iii Data collection

Data extraction forms will be developed and piloted building on the variables we defined in our earlier reviews. Data will be extracted independently and compared convened by a third investigator (co-investigator KI). If there is more than one psychological intervention group eg a three or four arm controlled trial, we will include all but use the most intensive intervention as the primary experimental group for the primary meta-analysis. Network analyses will allow us to compare the multiple arms so that data is not wasted. Data will be extracted and coded in a standardised manner on the following:

a) publication characteristics: year of publication, publication type (peer review or not), country of origin, health care setting, language, funding source.

b) patient characteristics: type of diabetes, lifespan status, average age, gender distribution, ethnicity distribution, socioeconomic setting, duration of diabetes, complications status, average glycaemic control, receipt of structured education, other clinical features such as obesity, medications (for T1DM: multiple injections or CSII and for T2DM: lifestyle advice, antidiabetes medications and/or insulin therapy).

c) we will extract the following components of the intervention: type of therapy, theoretical framework, use of manual, specialty of therapist, training of therapist, competency assessment of therapist, description of any specific behavior change techniques, number of sessions, duration of therapy, format of delivery (face to face, online, telephone, text messaging) and whether individual, group or family/couple, length of follow up from baseline, use of booster or maintenance sessions.

d) outcome characteristics: HbA1c, measures of behaviour change or self management, psychological measures, quality of life, at baseline and follow up (or mean change).

e) economic data: the costing of the interventions will be identified. We will extract evidence on resource use in both intervention arms and comparator (usual care) arms from all of the studies included in the effectiveness review. Typically, some description of the staff grade and time for different components of the intervention are included into the description of the intervention arm in a clinical study, for example an RCT. It is often the case that there is less clarity on the comparator arm with a minimal description of standard or usual care. We will extract all information available for the studies. We will contact investigators to obtain any further detail on resource use that might not be available in the published study papers. Having collected the available data on resource use, we will undertake a workshop with clinical advisors (co led with co applicant SH), to formulate a costing for each intervention that is relevant and appropriate to current UK practice. This will include estimating the time and grades of staff input and any non staff related costs. These resource use estimates will be multiplied by standard unit costs (86) and NHS reference costs. This process will provide base case cost estimates for each intervention to be examined. Having developed these, we will share them with the clinical experts for assessment of face validity and also to identify uncertainties in these costings for use in scenario analyses within the cost-effectiveness modelling. Through Prof Heller's contacts with many UK diabetes departments we will also be able to gain insight from other centres as to the robustness of these costings.

5.5 Data items: all variables and its categories for the data collected will be listed and defined *a priori* taking into account pre-planned data assumptions and simplifications.

5.6 Quality assessment of bias

There are many scales and checklists to assess the risk of bias in the methods used in the conduct of controlled trials. For RCTs, we will use the current Cochrane Handbook Tool for Risk of Bias (87). For non randomised controlled trials there is no consensus on guidance for assessing risk of bias but the Cochrane Collaboration will be publishing guidance (88). If this is not available we will use the Newcastle-Ottawa Scale (89).

5.7 Data synthesis

5.7.i Systematic review

A standardised structured synthesis of all studies included in the systematic review will be conducted. In those studies which do not contain sufficient data to be pooled in the meta-analysis, we will give a narrative synthesis.

5.7. ii Meta-analysis

The mean difference in change between baseline and follow-up scores between the two groups will be standardised by calculating Cohen's d, the difference between the two raw means divided by the pooled standard deviation of the difference as recommended by Borenstein et al (90). Hedges g bias correction for small sample sizes will be applied will be used for data where individual patient data are available. The effect size will be calculated from the raw data or otherwise published summary data will be used. The standardised effects will be pooled using an inverse variance–weighted random-effect model, which assumes in addition to within-group variability that the mean effects differ across studies (between study heterogeneity) which is expected due to the variety of case mix and settings. The presence of publication or other bias will be assessed by visual inspections of funnel plots and the effect of possible bias will be assessed in sensitivity analyses using Duval and Tweedie non-parametric 'trim and fill' method (91). Meta-regression will be used to investigate differences between types of treatment and the possible effects of age of study and study quality (91). Meta-analysis will be performed using STATA 14 (92). We have the original data files from the 2003 systematic review. This means we are able to present the combined data for new and old systematic reviews in chronological order. We will also present the findings of the new systematic review separately. This will enable us to demonstrate whether research evidence in the last 10 years is more or less effective compared to what has gone before.

5.7.iii Individual participant meta-analysis

Where we have access to individual participant data for the included studies we will conduct a one stage meta-analysis based on a standard multi-level regression analysis which allows to incorporate random effects for heterogeneity (93, 94). Individual participant meta-analyses has the advantage of allowing the use of individual patient characteristics, such as gender and age, to be included in the analysis and thus avoids biases associated with use of aggregate data in meta-regression (93). We will limit the IPD meta-analysis to work published since the 2003 systematic review. Because it is unlikely we would obtain all datasets, we will assess any differences between studies that provided individual participant data and studies where we could not obtain individual participant data for potential biases and determine whether conclusions of the meta-analysis might change if those studies not providing individual participant data had been included (95).

5.7.iv Sensitivity and subgroup analyses

We will conduct meta-regression to determine whether factors such as number of sessions attended, duration and type of therapy, socio-economic or cultural factors, and behaviour change techniques are independently associated with changes in self-management or glycaemic control.

5.7.v Assessment of bias

The presence of publication or other bias will be assessed by visual inspections of funnel plots (96) and the effect of possible bias will be assessed in sensitivity analyses using Duval and Tweedie (2000) non-parametric 'trim and fill' method (89, 97). Meta-regression will be used to investigate the possible effects of age of study and study quality, and compared with the data pooled for the earlier reviews (50, 51).

5.7.vi Network meta-analysis

Standard meta-analysis methods for clinical trials focus on comparisons of two interventions between treatment and healthy control or placebo group, or a new intervention versus standard practice. However, in some studies more than two interventions may have been used and they do not always have similar control groups. We therefore will extend the meta-analyses by performing indirect comparisons by applying network meta-analyses which allow the simultaneous analysis of clinical trials involving different treatments or control groups (98). Unlike traditional meta-analysis, which summarise the results of trials that have evaluated the same treatment/placebo combination, network meta-analyses allows comparing results from two or more studies that have one treatment in common. Multivariate random-effects meta-regressions, will be used to estimate consistency and inconsistency models which allow an assessment of the extent to which different sources of evidence are compatible (99). Network meta-analysis will be done using the user-written STATA function mvmeta (100).

5.7.vii Modelling cost-effectiveness

The University of Sheffield already has two well developed cost-effectiveness models, one for T1DM and one for T2DM, both of which have been used in previous NIHR / NCCHTA assessments of the cost-effectiveness of a number of interventions. Both will be used in this project. We will specifically request access to anonymised individual data from each included study to include at a minimum but not exclusively, the following variables: type of diabetes; age of participant; baseline and follow-up HbA1c. Patient level simulation models can be data hungry but the Sheffield Type 1 and Type 2 Diabetes Models have been built to incorporate evidence flexibly. Where individual level data is available this will be utilised directly. Where aggregate level evidence is available e.g. from meta-analyses or single published studies then the model is built to incorporate probability distributions based on the published evidence. This includes central estimates and parameter uncertainty (to enable probabilistic sensitivity analysis) and where possible / necessary, the statistical modelling of patient level heterogeneity.

T1DM modelling

The Sheffield Type I diabetes model (ST1DM) has been developed over the last 5 years primarily to examine the cost-effectiveness of structured education (101). It has been used to examine the cost-effectiveness of the Dose Adjustment for Normal Eating (DAFNE) intervention as part of an NIHR programme grant (102-104).

The ST1DM model is an individual level simulation model, which simulates a number of individuals, say 10000, modelling each person's trajectory of risk factors, including HbA1c (the main driver of the probability of many of the clinical outcomes) , blood pressure, and lipids. The occurrence of events is modelled probabilistically with occurrence of hypoglycaemia and diabetic keto-acidosis included, as well as micro-vascular (neuropathy, nephropathy, retinopathy) and macro-vascular (MI and stroke) events modelled. Each type of event can have an effect on cost and health related quality of life measured

primarily using EQ-5D derived utilities for T1DM patients using the DAFNE database. This model assesses the longer-term incremental cost per quality adjusted life year gained of each intervention versus usual care.

Because the main study evidence will cover effects on HbA1c, hypoglycaemia and diabetes ketoacidosis (DKA) rates in the short term e.g. 6 months or 12 months, it is important to examine assumptions regarding longer-term sustained effects of the psychological interventions on these clinical parameters. It is therefore helpful that the evidence review team will also be examining longer term observational study evidence because this will inform these parameters / assumptions in the cost-effectiveness modelling.

T2DM modelling

The Sheffield Type 2 Diabetes Policy Model (ST2DM) has been developed over the last 12 years to examine the cost-effectiveness of treatments and screening and prevention strategies in T2DM. Interventions examined include drug treatments (including sequential strategies), education programmes (including the DESMOND course (105)) and diabetes and pre-diabetes screening and treatment strategies work undertaken for the NICE public health programme (106) and the NIHR HTA programme (107, 108) .

The diabetes treatment model has a similar framework to that above for T1DM. It is also an individual level simulation model, with trajectories for HbA1c, blood pressure and lipids, and also models hypoglycaemia, DKAs, micro- and macro-vascular events, all using evidence on the occurrence of these events based on T2DM evidence. These are partly based on the UKPDS related studies (109-111) but also extends this with additional international evidence where required. The ST2DM model can also produce estimates of long-term cost-effectiveness in terms of incremental cost per life year gained.

Short-term utilities

Typically, there are two aspects to short term improvements in HRQoL. One is general improvements in health and the other is the utility values associated with diabetic complications.

The first of these aspects, HRQoL improvements due to improvements in health, will be considered for incorporation into the economic analyses, but there will be challenges in doing so given limited evidence and reporting. If an intervention reports health related quality of life (HRQoL) effects using a generic preference based measure that can be used to calculate a quality adjusted life year (QALY), then we will incorporate this evidence. If HRQoL is measured using a disease specific instrument which can be mapped to a generic preference based HRQoL measure, then we will incorporate this evidence. However, it is unlikely that such evidence will be available for all interventions. Where evidence is unavailable, we will consider undertaking an expert elicitation process to obtain expert judgement on the likely scale of HRQoL effects. If interventions are considered by clinical experts to be similar in structure to other interventions then, we will consider assuming the same scale of HRQoL improvement as is evidenced in other studies. If interventions are considered by the experts to be very different in structure then we will elicit expected HRQoL improvement relative to other similar interventions (including eliciting the expert's uncertainty in HRQoL effect.

The second aspect is short term (e.g. within one year) occurrence of complications / adverse events. The values currently used in the Sheffield Type 1 diabetes model are reported in Table 33 of Heller *et al*. (104) and the values currently used in the Sheffield Type 2 diabetes model are reported in Table 23 of Gillet *et al (112)*. Whether the values reported in Heller *et al*. and Gillet *et al*. need to be updated will be considered when the review of economic evaluation studies is conducted.

Health Economic Decision Modelling Analysis Plan (HEDMAP)

Before final analyses are conducted, we will undertake a further review of both models and the assumptions used within them regarding trajectories, probabilities of event, unit costs of events, utilities etc. Although both models have been developed for some time and used for health technology assessments on several occasions, they have not been used at the same time within the same project before, and it will be useful to align and update assumptions on key model parameters. We plan to focus our review of the cost-effectiveness studies literature around: 1. costs of interventions, specifically psychological interventions; 2. costs of diabetes complications; 3. utility values for health states; and 4. disease progression models and risk equations

The analysis will then develop base case estimates of cost-effectiveness of each psychological intervention versus usual care. The perspective will be the UK NHS setting. Long-term costs and benefits will be discounted as per the NICE reference case. We will account for parameter uncertainty using probabilistic sensitivity analysis. We will also use the new Sheffield Accelerated Value of Information (SAVI) approach to estimate overall EVPI and expected value of perfect parameter information (EVPPI) which will enable an understanding of how uncertain we are about cost-effectiveness and help to inform priorities for any further research that would be useful to reduce uncertainty in specific parameters of the model e.g. are further short-term efficacy trials needed, or more long-term follow up, or more data on the costs or utilities to reduce decision uncertainty? Scenario analyses will also be undertaken, especially with regard to intervention costs in order to answer the question, what level of investment can be made (per person) in terms of psychological intervention in order for them to be considered cost-effective?

The resulting analyses will be published as part of the proposed HTA monograph and as a peer-reviewed journal article.

5.7.viii Confidence in synthesized evidence

Grading of Recommendations Assessment, Development and Evaluation (GRADE) will be used to determine the quality of the evidence of the outcomes under investigation and subsequent translational strength of recommendations for clinical practice (113).

6. DISSEMINATION AND PROJECTED OUTPUTS

6.1 Dissemination

To ensure that potential practice recommendations from the systematic review are adopted we would provide an executive summary in the form of prioritised evidence based interventions that have some evidence for effectiveness and which have the potential to be implemented. We would share the summary with local and national stakeholders who will have contact with diabetes health professionals. The findings will also be disseminated via the following:

6.1.i South London Health Innovation Network (HIN), is part of the Academic Health Sciences Network (AHSN). The South London HIN diabetes clinical programme has 3 main areas of focus: a) supporting better self-management; b) enabling systems for better integration of care; and c) adopting new technologies. Therefore this evidence synthesis fits within the HIN's remit and will allow for dissemination to local commissioners, clinicians and academics working within diabetes.

6.1.ii Diabetes and Obesity ‘Action for Diabetes’ NHS England. This research will be disseminated via regional diabetes strategic network. This strategic partnership will provide wider dissemination

opportunities and ensure that research outputs of clinical importance can be used to develop clinical pathways and interventions to support self-management for people with diabetes for the whole of London.

6.1.iii Social media. The aim is to publicise the results of the project via social media and networks such as the Diabetes Online Community (DOC).

6.1.iv Peer-reviewed journals. This research proposal would generate 3 stand-alone reports (protocol paper, efficacy paper, cost-effectiveness paper) that will be submitted as research articles to peer-reviewed health journals.

6.1.v National and international conferences such as Diabetes UK and Association of British Clinical Diabetologists. This work will be presented to fellow academics and clinicians at diabetes and public health meetings.

6.1.vi Local and national clinical networks. This work will be disseminated locally via the London Strategic network, regional diabetes psychology network and nationally via the British Psychological Society, Royal College of Psychiatrists, Royal College of General Practitioners, diabetes and practice nurse forums and the Association of British Clinical Diabetologists.

6.2 Projected outputs

6.2.i NICE Guidance

We would anticipate the systematic review would add to the evidence base for structured education programmes and provide evidence to support the wider introduction of psychological/motivational interventions for people with diabetes to improve their self-management.

6.2.ii HIN toolkits

The systematic review would add to the evidence base of the HIN's diabetes project areas regarding structured education and their insulin themed project.

6.2.iii London Strategic Health Network. Dissemination via this network would ensure that the systematic review would be used to develop clinical pathways and interventions to support self-management for people with diabetes for the whole of London.

6.2.iv Diabetes UK. This systematic review may be used to campaign for improved access to non-pharmacological approaches to diabetes self-management.

6.2.v HTA report: A full report with the executive summary will be sent to all NHS authorities

6.2.vi Post publication: generate new hypotheses and develop and evaluate new health technologies in light of findings.

7. PLAN OF INVESTIGATION AND TIMETABLE

Activity	-1	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18
Recruit RA	■	■																	
Train RA			■																
Scoping review		■	■																
Generate search strategy		■	■	■															
Protocol development and registry with PROSPERO				■	■	■	■												
Database search refine search strategy							■	■	■										
Economic strategy										■	■								
Title review							■	■	■										
Abstract review full text retrieval							■	■	■	■	■	■							
Data extraction										■	■	■							
Contact authors for data and grey literature							■	■	■	■	■	■							
Quality assessment of included studies													■	■					
Narrative synthesis														■	■	■			
Meta-analysis														■	■	■			
Cost-effectiveness analysis														■	■	■			
Report writing																	■	■	■
Dissemination																	■	■	■

8. PROJECT MANAGEMENT

The PI will coordinate activity in order to deliver the project milestones. The administrator will assist the PI in the recruitment of the research assistant (RA) and will be responsible for arranging meetings and recording all correspondence from these and project teleconferences. The PI will be responsible for training and supervision of the RA. In the initial 3 months of the project the project team will have frequent teleconferences, weekly to begin with, to discuss the proposed protocol and at an early stage hold the first face-to-face meeting. Once the protocol is agreed the PI and RA will report progress every 2 weeks by email to the rest of the team. Following the trial of search strategy and once the scoping review is complete and the main database searches have been run the RA and PI will independently review the abstracts for inclusion and if abstracts cannot be excluded full texts will be retrieved and read in full to determine whether the studies meet inclusion criteria. Disagreement will be resolved by KI who will

independently review the studies. Following this the health economics strategy for determining cost-effectiveness will be planned and a further meeting arranged. The third face-to-face meeting will take place at the data synthesis stage to discuss the strategy for reporting the results and the meta-analysis, and more frequent teleconferences and tasks distributed to ensure timely report writing.

9. PATIENT PUBLIC INVOLVEMENT (PPI)

a. Proposed PPI, local and national membership

i. We will establish a local membership team which will consist of one adult member with Type 2 diabetes, one adult member with Type 1 diabetes, and one young person with diabetes and/or a parent/carer who will be recruited via our diabetes service at King's Health Partners. Local members will be invited to participate in project meetings throughout the course of the study.

ii. We will also seek national representation via the NHS England diabetes Clinical Reference Groups who will forward our invitations for membership. We will ask for comments on key documents via email, such as the research questions and data extraction sheets (see section b., below). We will hold 2 focus groups, one in the north of England (Sheffield), and one in the south (London). These will be purposively sampled groups of 6-10 people with diabetes. The aim of the focus groups will be to determine patient views on the research to date/review findings and how the findings should be disseminated and translated (see section b. below).

j. PPI components

i. Face validity of methods used.

-We will seek PPI on the research questions being asked in terms of the relevance to patients and public and whether there are any additional questions which need to be addressed at protocol development. This process would start in June 2015 at our next local CRN diabetes PPI meeting and nationally via email at the same time in partnership with NHS England.

-We will seek national and local PPI on the data extraction tool to be used to ensure that all data of interest to patients and the public is being collected.

-We will seek the distinction from a patient's perspective of a psychological treatment versus an educational treatment.

ii. Interpretation, dissemination and translation.

We will establish via the focus groups PPI on the preliminary results from the systematic review. For example: 1.do these findings convince patients with diabetes and their carers whether psychological interventions are of benefit and if so, what for; 2. how the results of this study should be shared, such as via social media; 3. whether they would like to recommend that psychological therapies should be available in routine clinical care; and 4. their preference in terms of the therapeutic style/components used, their opinion of the training of the therapists delivering the intervention, their opinion on the duration and intensity of the therapy, and the mode of delivery such as group, individual, or family.

10. EXPERTISE

Kirsty Winkley has conducted 7 systematic reviews (6 published) and as the PI will lead, coordinate and take responsibility for the conduct of this project to within the agreed time-frame. She will develop the protocol for the systematic review and supervise the RA to determine search strategy and play a key role in identifying and selecting the studies for inclusion in the systematic review.

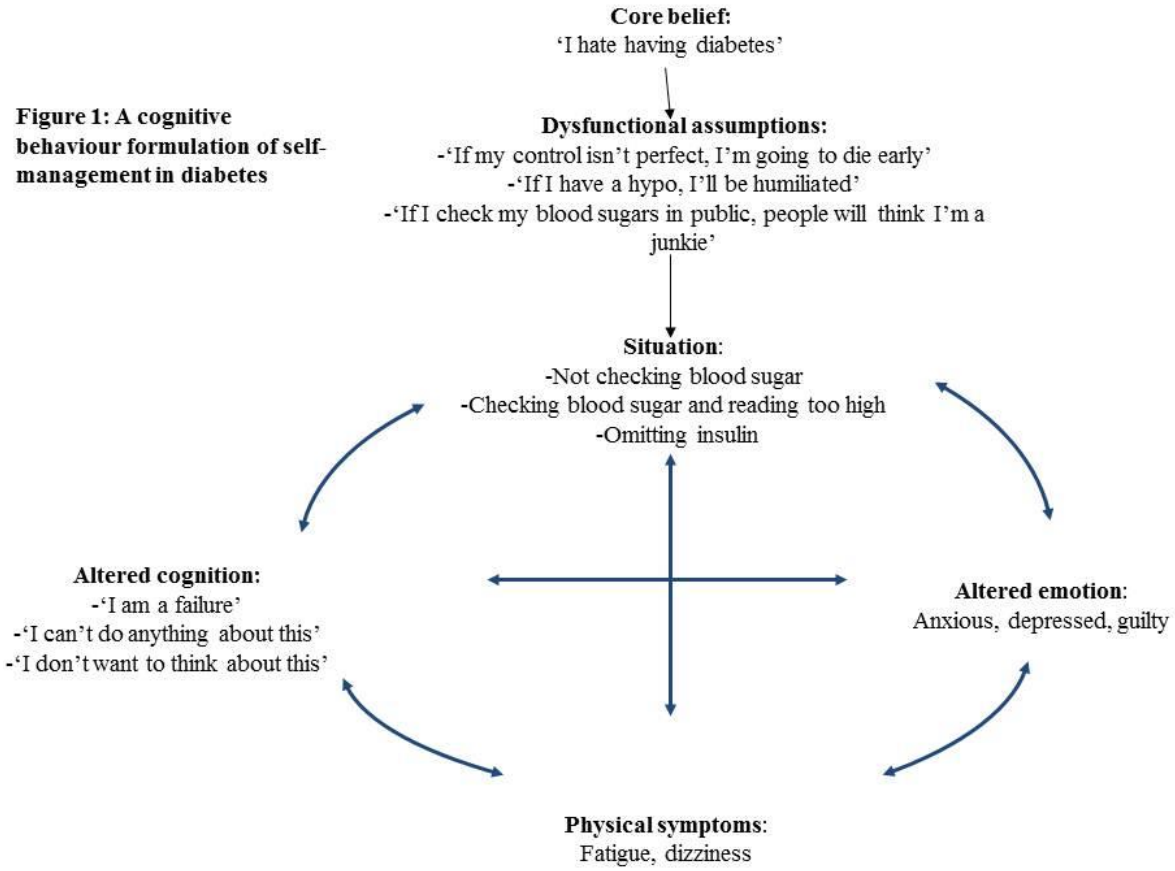
Khalida Ismail is a senior clinical academic in diabetes psychiatry, epidemiology and clinical trials who has a national and international track record in developing and evaluating all types of psychological interventions to support self-diabetes management (CBT, motivational interviewing, psycho-analytical, family, e-health, self help, text messaging) for both T1DM and T2DM across the lifespan, and translating research (including NIHR funded) into award winning services (BMJ Diabetes Team 2014). She will provide advice on the psychological models and support networking, review methodology, resolving differences in eligibility and descriptions of studies.

Simon Heller is an experienced clinician, diabetes specialist and clinical investigator with particular expertise in studying the development of complex educational interventions to improve diabetes self - management. He led the DAFNE RCT which demonstrated improved glycemic control and improved quality of life up to a year. He has extensive experience of translating research findings such as DAFNE leading the recommendation that all individuals with diabetes should have access to structured education programmes and it was acknowledged by NICE. He was lead investigator for an NIHR programme grant exploring different aspects of self-management in relation to the DAFNE course. He has led the development of courses for adolescents (KICK-OFF and WICKED) in collaborative projects with Sheffield Children's Hospital and the Dept of Psychology, University of Sheffield and was a co-investigator for the DESMOND trial which developed and trailed interventions for newly diagnosed adults with type 2 diabetes.

Alan Brennan is an experienced diabetes health economist and has been involved in modelling the cost-effectiveness of interventions for T1DM and T2DM for many years. He will supervise collection of the economic data and will be responsible for conducting the economic analysis including the modelling. He will lead on the summary of the health economic outputs.

Daniel Stahl is a Senior Lecturer in Biostatistics in the Department of Biostatistics of the IoPPN and affiliated with the KCL Clinical Trials Unit. He is a trial statistician in three NIHR funded RCTs, including two programme grants in which Dr Winkley is also involved. He is experienced in the meta-analyses of studies in mental health. He will supervise the data extraction and meta-analyses and will perform the network meta-analyses.

Figure 1: A cognitive behaviour formulation of self-management in diabetes



1. Turner RC, Cull CA, Frighi V, R.R. H, U.P.D.S G. Glycemic control with diet, sulfonylurea, metformin, or insulin in patients with type 2 diabetes mellitus: progressive requirement for multiple therapies (UKPDS 49). Jama. 1999;281(21):2005-12.
2. NICE. Type 2 Diabetes - newer agents (partial update of CG66) (CG87) 2009. Available from: http://www.nice.org.uk/cg87.
3. NICE. Type 1 diabetes: management of type 1 diabetes in adults in primary and secondary care. London: NICE, 2004.
4. DAFNE. Training in flexible, intensive insulin management to enable dietary freedom i people with type 1 diabetes: dose adjustment for normal eating (DAFNE) randomised controlled trial. BMJ. 2002;325:1-6.
5. Everett J, Jenkins E, Kerr D, Cavan DA. Implementation of an effective outpatient intensive education programme for patients with type 1 diabetes. Practical Diabetes International. 2003;20(2):51-5.
6. Davies MJ, Heller S, Skinner TC, Campbell MJ, Carey ME, Cradock S, et al. Effectiveness of the diabetes education and self management for ongoing and newly diagnosed (DESMOND) programme for people with newly diagnosed type 2 diabetes: cluster randomised controlled trial. BMJ. 2008 2008-02-28 23:01:30;336(7642):491-5.
7. Deakin TA, Cade JE, Williams R, Greenwood DC. Structured patient education: the Diabetes X-PERT Programme makes a difference. Diabetic Medicine. 2006;23(9):944-54.
8. Hopkins D, Lawrence I, Mansell P, Thompson G, Amiel S, Campbell M, et al. Improved biomedical and psychological outcomes 1 year after structured education in flexible insulin therapy for people with type 1 diabetes the UK DAFNE experience. Diabetes Care. 2012;35(8):1638-42.
9. Khunti K, Gray LJ, Skinner T, Carey ME, Realf K, Dallosso H, et al. Effectiveness of a diabetes education and self management programme (DESMOND) for people with newly diagnosed type 2 diabetes mellitus: three year follow-up of a cluster randomised controlled trial in primary care. BMJ. 2012 2012-04-26 23:32:23;344.
10. HSCIC. Health and Social Care Information Centre. National Diabetes Audit 2010-2011. Report into the data quality of Diabetes Structured Education. 2012 [28th February 2014]. Available from: http://www.hqip.org.uk/assests/NCAPOP-Library/NCAPOP-2012-13/Diabetes-Audit-Report-10-11-StructuredEducation-pub-2012.pdf.
11. HSCIC. National Diabetes Audit 2012-2013 2014 [12.01.2015]. Available from: http://www.hscic.gov.uk/catalogue/PUB14970/nati-diab-audi-12-13-care-proc-rep.pdf.
12. Anderson RJ, Freedland KE, Clouse RE, Lustman PJ. The prevalence of co-morbid depression in adults with diabetes. Diabetes Care. 2001;6:1069-78.
13. Barnard K, Skinner T, Peveler R. The prevalence of co-morbid depression in adults with type 1 diabetes: systematic literature review. Diabetic Medicine. 2006;23:445-8.
14. Ali S, Stone M, Peters J, Davies M, Khunti K. The prevalence of co-morbid depression in adults with type 2 diabetes: a systematic review and meta-analysis. Diabetic Medicine. 2006;23:1165-73.
15. Lin EHB, Katon W, Von Korff M, Rutter C, Simon GE, Oliver M, et al. Relationship of Depression and Diabetes Self-Care, Medication Adherence, and Preventive Care. Diabetes Care. 2004 September 1, 2004;27(9):2154-60.
16. Fisher L, Mullan JT, Arean P, Glasgow RE, Hessler D, Masharani U. Diabetes Distress but Not Clinical Depression or Depressive Symptoms Is Associated With Glycemic Control in Both Cross-Sectional and Longitudinal Analyses. Diabetes Care. 2010 January 1, 2010;33(1):23-8.
17. Lustman PJ, Anderson RJ, Freedland KE, De Groot M, Carney RM, Clouse RE. Depression and poor glycemic control. A meta-analytic review of the literature. Diabetes Care. 2000;23:934-42.

18. DeGroot M, Anderson RM, Freedland KE, Clouse RE, Lustman PJ. Association of depression and diabetes complications: a meta-analysis. Psychosomatic Medicine. 2001; 63:619-30.
19. Park M, Katon WJ, Wolf FM. Depression and risk of mortality in individuals with diabetes: a meta-analysis and systematic review. General Hospital Psychiatry. 2013;35(3):217-25.
20. Ismail K, Winkley K, Stahl D, Chalder T, Edmonds M. A cohort study of people with diabetes and their first foot ulcer: the role of depression on mortality. Diabetes Care. 2007;30:1473-9.
21. Rodin GM, Daneman D, Johnson LE, Kenshole A, Garfinkel P. Anorexia nervosa and bulimia in female adolescents with insulin dependent diabetes mellitus: A systematic study. Journal of Psychiatric Research. 1985;19(2):381-4.
22. Goebel-Fabbri AE, Fikkan J, Franko DL, Pearson K, Anderson BJ, Weinger K. Insulin restriction and associated morbidity and mortality in women with type 1 diabetes. Diabetes Care. 2008;31(3):415-9.
23. Fisher L, Glasgow RE, Mullan JT, Skaff MM, Polonsky WH. Development of a Brief Diabetes Distress Screening Instrument. The Annals of Family Medicine. 2008 May 1, 2008;6(3):246-52.
24. Greenhalgh T, Helman C, Chowdhury AMm. Health beliefs and folk models of diabetes in British Bangladeshis: a qualitative study. BMJ. 1998 1998-03-28 00:00:00;316(7136):978-83.
25. Winkley K, Evwierhoma C, Amiel SA, Lempp HK, Ismail K, Forbes A. Patient explanations for non-attendance at structured diabetes education sessions for newly diagnosed Type 2 diabetes: a qualitative study. Diabetic Medicine. 2014:n/a-n/a.
26. Hool N. BABCP Core Curriculum Reference Document. 2010 [10.01.2015]. Available from: https://www.babcp.com/files/About/BABCP-Core-Curriculum-V2-190913.pdf.
27. RCPSYCH. Royal College of Psychiatrists - Psychotherapies 2014 [10.01.2015]. Available from: http://www.rcpsych.ac.uk/healthadvice/treatmentswellbeing/psychotherapies.aspx.
28. Abraham C, Michie S. A taxonomy of behavior change techniques used in interventions. Health Psychology. 2008;27:379 - 87. PubMed PMID: doi:10.1037/0278-6133.27.3.379.
29. Candy J, Balfour F, Cawley R, Hildebrand H, Malan D, Marks I, et al. A feasibility study for a controlled trial of formal psychotherapy. Psychological medicine. 1972;2(04):345-62.
30. Moran G, Fonagy P, Kurtz A, Bolton A, Brook C. A controlled study of the psychoanalytic treatment of brittle diabetes. Journal of the American Academy of Child & Adolescent Psychiatry. 1991;30(6):926-35.
31. Ciechanowski PS, Hirsch IB, Katon WJ. Interpersonal predictors of HbA1c in patients with type 1 diabetes. Diabetes Care. 2002;25(4):731-6.
32. Churchill R, Hunot V, Corney R, Knapp M, McGuire H, Tylee A, et al. A systematic review of controlled trials of the effectiveness and cost-effectiveness of brief psychological treatments for depression. Health Technology Assessment. 2002;5(35):1-173.
33. Gregg JA, Callaghan GM, Hayes SC, Glenn-Lawson JL. Improving diabetes self-management through acceptance, mindfulness, and values: a randomized controlled trial. Journal of consulting and clinical psychology. 2007;75(2):336.
34. Rogers C. On Becoming a Person: A Therapist's View of Psychotherapy. London: Constable; 1961.
35. Burke B, Arkowitz H, Mencola M. The efficacy of motivational interviewing: A meta-analysis of controlled clinical trials. Journal of Consulting and Clinical Psychology 2003;71:843-61.
36. Miller W, Rollnick S. Motivational interviewing: preparing people to change addictive behaviour. ed. 2nd ed. New York: Guildford Press; 2002.
37. Miller W, Rollnick S. Motivational interviewing: helping people change. 3rd ed. New York: Guilford Press; 2013.
38. Rubak S, Sandbæk A, Lauritzen T, Christensen B. Motivational interviewing: a systematic review and meta-analysis. British Journal of General Practice. 2005;55:305-12.
39. Klerman GL, Weissman MM. New applications of interpersonal psychotherapy: American Psychiatric Pub; 1993.

40. Fosbury JA, Bosley CM, Ryle A, Sönksen PH, Judd SL. A trial of cognitive analytic therapy in poorly controlled type I patients. Diabetes Care. 1997;20(6):959-64.
41. Carr A. The effectiveness of family therapy and systemic interventions for child-focused problems. Journal of Family Therapy. 2009;31(1):3-45.
42. Pennebaker JW, Seagal JD. Forming a story: The health benefits of narrative. Journal of clinical psychology. 1999;55(10):1243-54.
43. Kellermann PF. Focus on psychodrama: The therapeutic aspects of psychodrama: Jessica Kingsley Publishers; 1992.
44. Malchiodi CA, Malchoidi CA. The art therapy sourcebook: Lowell House Los Angeles; 1998.
45. Nobis S, Lehr D, Ebert D, Berking M, Heber E, Baumeister H, et al. Efficacy and cost-effectiveness of a web-based intervention with mobile phone support to treat depressive symptoms in adults with diabetes mellitus type 1 and type 2: design of a randomised controlled trial. BMC Psychiatry. 2013;13(1):306. PubMed PMID: doi:10.1186/1471-244X-13-306.
46. van Bastelaar KM, Pouwer F, Cuijpers P, Riper H, Snoek FJ. Web-based depression treatment for type 1 and type 2 diabetic patients a randomized, controlled trial. Diabetes Care. 2011;34(2):320-5.
47. Hampson SE, Skinner TC, Hart J, Storey L, Gage H, Foxcroft A, et al. Effects of educational and psychosocial interventions for adolescents with diabetes mellitus: a systematic review. York: Health Technology Assessment, 2001.
48. Norris SL, Engelgau MM, Narayan KV. Effectiveness of self-management training in type 2 diabetes a systematic review of randomized controlled trials. Diabetes Care. 2001;24(3):561-87.
49. Fisher EB, Thorpe CT, DeVellis BM, DeVellis RF. Healthy Coping, Negative Emotions, and Diabetes Management A Systematic Review and Appraisal. The Diabetes Educator. 2007;33(6):1080-103.
50. Ismail K, Winkley K, Rabe-Hesketh S. Systematic review and meta-analysis of randomised controlled trials of psychological interventions to improve glycaemic control in patients with type 2 diabetes. Lancet. 2004;363(1589-97).
51. Winkley K, Landau S, Ismail K. Psychological interventions to improve glycaemic control in type 1 diabetes: systematic review and meta-analysis of randomised controlled trials. British Medical Journal. 2006;333:65-8.
52. DARE. Database of Abstracts of Reviews of Effects (DARE) [10.01.2015]. Available from: http://www.crd.york.ac.uk/CRDWeb/.
53. Alam R, Sturt J, Lall R, Winkley K. An updated meta-analysis to assess the effectiveness of psychological interventions delivered by psychological specialists and generalist clinicians on glycaemic control and on psychological status. Patient Education and Counseling. 2009;75:25-36.
54. Cotter AP, Durant N, Agne AA, Cherrington AL. Internet interventions to support lifestyle modification for diabetes management: A systematic review of the evidence. Journal of Diabetes and its Complications. 2014 3//;28(2):243-51.
55. Pal K, Eastwood SV, Michie S, Farmer AJ, Barnard ML, Peacock R, et al. Computer-based diabetes self-management interventions for adults with type 2 diabetes mellitus. The Cochrane database of systematic reviews. 2013;3:CD008776. PubMed PMID: 23543567. Epub 2013/04/02. eng.
56. Avery L, Flynn D, van Wersch A, Sniehotta FF, Trenell MI. Changing Physical Activity Behavior in Type 2 Diabetes: A systematic review and meta-analysis of behavioral interventions. Diabetes Care. 2012 December 1, 2012;35(12):2681-9.
57. Bolen SD, Chandar A, Falck-Ytter C, Tyler C, Perzynski AT, Gertz AM, et al. Effectiveness and Safety of Patient Activation Interventions for Adults with Type 2 Diabetes: Systematic Review, Meta-Analysis, and Meta-regression. Journal of general internal medicine. 2014:1-11.
58. Armour TA, Norris SL, Jack L, Jr., Zhang X, Fisher L. The effectiveness of family interventions in people with diabetes mellitus: a systematic review. Diabetic medicine : a journal of the British Diabetic Association. 2005 Oct;22(10):1295-305. PubMed PMID: 16176186. Epub 2005/09/24. eng.

59. Murphy HR, Rayman G, Skinner TC. Psycho-educational interventions for children and young people with Type 1 diabetes. Diabetic Medicine. 2006;23(9):935-43.
60. Couch R, Jetha M, Dryden DM, Hooton N, Liang Y, Durec T, et al. Diabetes education for children with type 1 diabetes mellitus and their families. 2008.
61. MacMillan F, Kirk A, Mutrie N, Matthews L, Robertson K, Saunders DH. A systematic review of physical activity and sedentary behavior intervention studies in youth with type 1 diabetes: study characteristics, intervention design, and efficacy. Pediatric Diabetes. 2014;15(3):175-89.
62. Petrak F, Herpertz S, Albus C, Hirsch A, Kulzer B, Kruse J. Psychosocial factors and diabetes mellitus: evidence-based treatment guidelines. . Current Diabetes Reviews. 2005;1:255-70.
63. Atlantis E, Fahey P, Foster J. Collaborative care for comorbid depression and diabetes: a systematic review and meta-analysis. BMJ open. 2014;4(4):e004706.
64. Ismail K, Thomas SM, Maissi E, Chalder T, Schmidt U, Bartlett J, et al. Motivational Enhancement Therapy with and without Cognitive Behavior Therapy to Treat Type 1 Diabetes: A Randomized Trial. Ann Intern Med. 2008 November 18, 2008;149(10):708-19.
65. Ismail K, Maissi E, Thomas S, Chalder T, Schmidt U, Bartlett J, et al. A randomised controlled trial of cognitive behaviour therapy and motivational interviewing for people with type 1 diabetes mellitus with persistent sub-optimal glycaemic control: A diabetes and psychological therapies (ADaPT) study. Health Technology Assessment. 2010;14(22):1-127.
66. Patel A, Maissi E, Chang HC, Rodrigues I, Smith M, Thomas S, et al. Motivational enhancement therapy with and without cognitive behaviour therapy for Type 1 diabetes: economic evaluation from a randomized controlled trial. Diabetic Medicine. 2011;28(4):470-9.
67. Zoffmann V, Lauritzen T. Guided self-determination improves life skills with type 1 diabetes and A1C in randomized controlled trial. Patient Education and Counseling. 2006;64(1):78-86.
68. Snoek FJ, Ven NCWvd, Twisk JWR, Hogenelst MHE, Tromp-Wever AME, Ploeg HMvd, et al. Cognitive behavioural therapy (CBT) compared with blood glucose awareness training (BGAT) in poorly controlled Type 1 diabetic patients: long-term effects on HbA_{1c} moderated by depression. A randomized controlled trial. Diabetic Medicine. 2008;25(11):1337-42.
69. Amsberg S, Anderbro T, Wredling R, Lisspers J, Lins PE, Adamson U, et al. Experience from a behavioural medicine intervention among poorly controlled adult type 1 diabetes patients. Diabetes Research & Clinical Practice. 2009;84:76-83.
70. George J, Valdovinos A, Russell I, Dromgoole P, Lomax S, Torgerson D, et al. Clinical effectiveness of a brief educational intervention in Type 1 diabetes: results from the BITES (Brief Intervention in Type 1 diabetes, Education for Self-efficacy) trial. Diabetic Medicine. 2008;25(12):1447-53.
71. Nansel TR, Iannotti RJ, Simons-Morton BG, Pltonick LP, Clark LM, Zeitzoff L. Long-term maintenance of treatment outcomes: diabetes personal trainer intervention for youth with type 1 diabetes. Diabetes Care. 2009;32:807-9.
72. Wysocki T, Harris MA, Buckloh LM, Mertlich D, Lochrie AS, Mauras N, et al. Randomized trial of behavioral family systems therapy for diabetes. Diabetes Care. 2007;30:555-60.
73. Christie D, Thompson R, Sawtell M, Allen E, Cairns J, Smith F, et al. Structured, intensive education maximising engagement, motivation and long-term change for children and young people with diabetes: a cluster randomised controlled trial with integral process and economic evaluation-the CASCADE study. Health technology assessment (Winchester, England). 2014;18(20):1-202.
74. Espeland M. Reduction in Weight and Cardiovascular Disease Risk Factors in Individuals With Type 2 Diabetes: One-Year Results of the Look AHEAD Trial. Diabetes Care. 2007 March 15, 2007.
75. Tudor-Locke C, Bell R, Myers A, Harris S, Ecclestone N, Lauzon N, et al. Controlled outcome evaluation of the First Step Program: a daily physical activity intervention for individuals with type II diabetes. International journal of obesity. 2003;28(1):113-9.

76. Smith West D, DiLillo V, Bursac Z, Gore SA, Greene PG. Motivational interviewing improves weight loss in women with type 2 diabetes. Diabetes Care. 2007;30:1081-7.
77. Polonsky WH, Fisher L, Schikman CH, Hinnen DA, Parkin CG, Jelsovsky Z, 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 February 1, 2011;34(2):262-7.
78. Wegmann N, Jelsovsky Z, Rees C, Wagner R. Use of structured SMBG facilitates earlier initiation of insulin therapy in poorly controlled T2DM patients: Results from the STeP study. Diabetes. 2011 July;60:A314. PubMed PMID: 70628908.
79. NICE. Behaviour change: the principles for effective interventions 2007 2007 [09.01.2015]. Available from: http://www.nice.org.uk/guidance/ph6.
80. Craig P, Dieppe P, Macintyre S, Michie S, Nazareth I, Petticrew M. Developing and evaluating complex interventions: the new Medical Research Council guidance. BMJ. 2008;337.
81. Ridge K, Bartlett J, Cheah Y, Thomas S, Lawrence-Smith G, Winkley K, et al. Do the effects of psychological treatments on improving glycemic control in type 1 diabetes persist over time? A long-term follow-up of a randomized controlled trial. Psychosomatic Medicine. 2012;74(3):319-23.
82. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. Annals of internal medicine. 2009;151(4):264-9.
83. PROSPERO. International reister of prospective systematic reviews [11.01.2015]. Available from: http://www.crd.york.ac.uk/PROSPERO/.
84. SIGN. Scottish Intercollegiate Guidelines Network. Search filters for economic studies. [12.01.2015]. Available from: http://www.sign.ac.uk/methodology/filters.html#econ.
85. Byrt T, Bishop J, Carlin JB. Bias, prevalence and kappa. Journal of Clinical Epidemiology. 1993;46(5):423-9.
86. Curtis L. Unit costs of health and social care 2013 [12.01.2015]. Available from: http://www.pssru.ac.uk/project-pages/unit-costs/2013/.
87. Higgins JP, Green S. Cochrane handbook for systematic reviews of interventions: Wiley Online Library; 2008.
88. Sterne JA. Extending the Cochrane Risk of Bias tool to assess risk of bias in randomised trials with non-parallel-group designs, and non-randomised studies 2014 [11.01.2015]. Available from: http://methods.cochrane.org/projects-developments/extending-cochrane-risk-bias-tool-assess-risk-bias-randomised-trials-non-paral.
89. Wells G, Shea B, O'connell D, Peterson J, Welch V, Losos M, et al. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. 2000.
90. Borenstein M, Hedges LV, Higgins JP, Rothstein HR. Introduction to meta-analysis: John Wiley & Sons; 2011.
91. Duval S, Tweedie R. Trim and fill: a simple funnel-plot–based method of testing and adjusting for publication bias in meta-analysis. Biometrics. 2000;56(2):455-63.
92. Sterne JA, Bradburn MJ, Egger M. Meta–Analysis in Stata™. Systematic Reviews in Health Care: Meta-Analysis in Context, Second Edition. 2008:347-69.
93. Simmonds MC, Higginsa JP, Stewartb LA, Tierneyb JF, Clarke MJ, Thompson SG. Meta-analysis of individual patient data from randomized trials: a review of methods used in practice. Clinical Trials. 2005;2(3):209-17.
94. Higgins J, Whitehead A, Turner RM, Omar RZ, Thompson SG. Meta-analysis of continuous outcome data from individual patients. Statistics in Medicine. 2001;20(15):2219-41.
95. Riley RD, Lambert PC, Abo-Zaid G. Meta-analysis of individual participant data: rationale, conduct, and reporting. BMJ. 2010 2010-02-05 13:38:57;340.

96. Sterne JA, Egger M. Funnel plots for detecting bias in meta-analysis: guidelines on choice of axis. Journal of Clinical Epidemiology. 2001;54(10):1046-55.
97. Peters JL, Sutton AJ, Jones DR, Abrams KR, Rushton L. Performance of the trim and fill method in the presence of publication bias and between-study heterogeneity. Statistics in Medicine. 2007;26(25):4544-62.
98. Li T, Puhan MA, Vedula SS, Singh S, Dickersin K. Network meta-analysis-highly attractive but more methodological research is needed. BMC medicine. 2011;9(1):79.
99. White IR, Barrett JK, Jackson D, Higgins J. Consistency and inconsistency in network meta-analysis: model estimation using multivariate meta-regression. Research Synthesis Methods. 2012;3(2):111-25.
100. Chaimani A, Higgins JP, Mavridis D, Spyridonos P, Salanti G. Graphical tools for network meta-analysis in STATA. PLoS ONE. 2013;8(10):e76654.
101. Thokala P, Kruger J, Brennan A, Basarir H, Duenas A, Pandor A, et al. Assessing the cost-effectiveness of Type 1 diabetes interventions: the Sheffield Type 1 Diabetes Policy Model. Diabetic Medicine. 2014;31(4):477-86.
102. Kruger J, Brennan A, Thokala P, Basarir H, Jacques R, Elliott J, et al. The cost-effectiveness of the Dose Adjustment for Normal Eating (DAFNE) structured education programme: an update using the Sheffield Type 1 Diabetes Policy Model. Diabetic Medicine. 2013;30(10):1236-44.
103. Elliott J, Jacques R, Kruger J, Campbell M, Amiel S, Mansell P, et al. Substantial reductions in the number of diabetic ketoacidosis and severe hypoglycaemia episodes requiring emergency treatment lead to reduced costs after structured education in adults with Type 1 diabetes. Diabetic Medicine. 2014.
104. Heller S, Lawton J, Amiel SA, Cooke D, Mansell P, Brennan A. Improving management of type 1 diabetes in the UK: the Dose Adjustment For Normal Eating (DAFNE) programme as a research test-bed. A mixed-method analysis of the barriers to and facilitators of successful diabetes self-management, a health economic analysis, a cluster randomised controlled trial of different models of delivery of an educational intervention and the potential of insulin pumps and additional educator input to improve outcomes. Programme Grants Appl Res 2014;2(5).
105. Gillett M, Dallosso H, Dixon S, Brennan A, Carey M, Campbell M, et al. Delivering the diabetes education and self management for ongoing and newly diagnosed (DESMOND) programme for people with newly diagnosed type 2 diabetes: cost effectiveness analysis. BMJ. 2010;341.
106. Gillett M, Chilcott J, Goyder E, Payne N, Thokala P, Freeman C. Prevention of type 2 diabetes: risk identification and interventions for individuals at high risk - Economic Review and Modelling. Report for National Institute of Clinical Excellence (NICE). 2012.
107. Waugh N, Scotland G, Gillet M, Brennan A, Goyder E, Williams R, et al. Screening for type 2 diabetes: literature review and economic modelling. Health Technology Assessment. 2007.
108. Gillett M, Royle P, Snaith A, Scotland G, Poobalan A, Imamura M, et al. Non-pharmacological interventions to reduce the risk of diabetes in people with impaired glucose regulation: a systematic review and economic evaluation. Health Technology Assessment. 2012;16(33).
109. Kothari V, Stevens RJ, Adler AI, Stratton IM, Manley SE, Neil HA, et al. UKPDS 60 risk of stroke in type 2 diabetes estimated by the UK Prospective Diabetes Study risk engine. Stroke. 2002;33(7):1776-81.
110. Stevens RJ, Coleman RL, Adler AI, Stratton IM, Matthews DR, Holman RR. Risk factors for myocardial infarction case fatality and stroke case fatality in type 2 diabetes UKPDS 66. Diabetes Care. 2004;27(1):201-7.
111. Stevens RJ, Kothari V, Adler AI, Stratton IM, Holman RR, Group UKPDS. The UKPDS risk engine: a model for the risk of coronary heart disease in Type II diabetes (UKPDS 56). Clinical Science. 2001;101(6):671-9.

112. Gillett M BA, Watson P, Khunti K, Khunti K, Davies M, Davies M, Mostafa S & Gray LJ. The cost-effectiveness of testing strategies for type 2 diabetes: A modelling study. Health Technology Assessment. 2015;19(33):1-80.
113. Guyatt GH, Oxman AD, Vist GE, Kunz R, Falck-Ytter Y, Alonso-Coello P, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. BMJ. 2008;336(7650):924-6.