NCCHTA

18th April 2007

REVISED PROTOCOL: Version 2 – 18.08.03

1 PROJECT TITLE

A randomised controlled trial of cognitive behaviour therapy and motivational interviewing for people with Type 1 diabetes mellitus with persistent sub-optimal glycaemic control.

PLANNED INVESTIGATION

1. Objectives

1.1 We will use a three armed randomised controlled trial to test the effectiveness of cognitive behaviour therapy compared to motivational interviewing and usual care in helping patients with Type 1 diabetes improve their glycaemic control.

1.2 To examine the cost effectiveness of motivational interviewing and of cognitive behaviour therapy compared to usual care for improving glycaemic control.

1.3 To identify cognitive, behavioural and biological predictors of outcome.

2. Existing research

2.1 Clinical features of Type 1 diabetes

Type 1 diabetes (T1DM) is a chronic condition characterised by an absolute deficiency of insulin with an onset usually in childhood and early adulthood. Management requires the patient to self-administer insulin injections several times a day and adhere to diabetes specific dietary, exercise and self monitoring regimens. The aim is to achieve blood glucose levels to near as normal, as persistent hyperglycaemia and duration of diabetes increase the risk of developing diabetic complications (nephropathy, neuropathy and retinopathy) and early death. While well-controlled diabetes is not disabling complications early in life can be handicapping. Adherence to diabetes self care regimen is a critical factor contributing to poor glycaemic control.

2.2 Epidemiology

The prevalence of T1DM is around 3 per 10,000 per year and is rising.[1,2] The mortality rates are still unacceptably high especially in the young, women, materially deprived groups and ethnic minorities. In South Tees T1DM is associated with a 6- and 3-fold increase in all cause standardised mortality in women and men respectively compared to the local population[3] and material deprivation was associated with a doubling of mortality.[3] Individuals with T1DM from ethnic minority groups have a 2- fold increase in mortality.[4] Diabetes and its complications constitute around 5% of the National Health Service (NHS) budget.[5] Intensive medical regimens and strict control of blood glucose can reduce the rate of complications[6] but are costly[7] and improvements are not always sustained when the intensive regimen ends.[8]

2.3 Psychological factors associated with sub-optimal glycaemic control

Depressive disorders are more common in adolescents[9] and adults with T1DM than healthy controls.[10] In a recent meta-analysis, depression was associated with hyperglycaemia with a mild to moderate effect size.[11] Expressed emotion and family conflicts appear to be associated with poor control in prospective studies.[12] Eating disorders can be twice as common in women with T1DM than matched controls[13] and associated with a 3-fold risk for retinopathy.[14] In adolescence, there is often a worsening of glycaemic control[15] due to intense physiological[16] and psychological changes which may lead to reduced self-care, onset of eating problems and initiation of substance misuse. While some adolescents do overcome the turbulence, for a significant proportion adherence difficulties continue into adulthood.

2.4 Reviews of randomised controlled trials

Education and psychological interventions are the two most common non-pharmacological interventions studied in people with T1DM. They are often grouped together or described as 'psychosocial' but are different clinical specialities. Educational interventions are based on principles of learning that provide information, instruction, advice and support. On the other hand, psychological interventions aim to alter unhelpful affects, cognitions and/or behaviours using principles of psychotherapy, utilising the therapeutic alliance to facilitate change. Psychological services attached to diabetes teams are few and sporadic.[17]

Two well-conducted and inclusive reviews of educational and psychosocial interventions for adults[18] and adolescents[19] have concluded that psychological interventions may be effective but serious methodological flaws in individual studies limit their interpretation. A recent thorough systematic review and meta-analysis of controlled studies of behavioural interventions in adolescents with T1DM identified 24 randomised controlled trials (RCT) of educational or psychosocial interventions.[20] They reported a mean effect size of 0.3 for psychosocial and glycaemic control outcomes when only the RCTs were pooled. This effect size is equivalent to a modest 0.6% improvement in glycosylated haemoglobin (HbA_{1c}). Theoretically based interventions were more effective. There were some limitations to this analysis. First, educational and psychological interventions that may be different clinical disciplines were pooled together which may have increased the heterogeneity of the pooled sample. Second, the results of the meta-analysis may be limited as control groups for two studies[21,22] were used twice in the same analysis. Third, the HbA_{1c} values of one study was not used to calculate the pooled effect size.[23] Fourth, as the object of the review was limited to adolescents with T1DM, the results could not be generalised to an adult population with T1DM.

We carried out an independent systematic review of RCTs of psychological interventions for improving glycaemic control in patients with diabetes based on a Cochrane Collaboration protocol.[24] We limited our review to RCTs as these are the most rigorous we wish to compare ours with. We excluded interventions that were based on education theory. We included adults and adolescents. We identified 11 RCTs in people withT1DM. The interventions that were being tested included social learning;[25] multi-family group therapy;[22] problem solving[26] and self-management training[27] in families where patient and parents are seen in separate groups; family therapy;[23,28] patient empowerment;[29] problem solving in individuals;[30] cognitive analytic therapy; [31] relaxation therapy;[32] and stress management.[33] When these studies were pooled we derived an effect size of 0.1 (95% confidence interval -0.7 to 0.9) for improvement in HbA_{1c}. We used a random effects model as there was evidence of significant heterogeneity in the fixed effect model ($Q=15.16$, $p=0.02$). We could not conclude from our meta-analysis that the psychological models are effective in improving glycaemic control, although the upper limit of the confidence interval suggests that they could potentially be very effective.

2.5 Limitations of previous studies

Few studies were based on representative samples of people with T1DM. Three studies defined the clinic population from which eligible patients were sampled, such as incident cases[23] or screening clinic lists.[28,31] Most studies used convenience sampling such as advertisements,[26] referrals from clinics[22,27] or gave insufficient detail.[30,32,33] Convenience sampling would result in recruiting patients and families motivated to change and more likely to improve. Patients who were having difficulties with their diabetes self-care but not in a state of readiness to change would be excluded.

Most studies did not recruit people from ethnic minorities despite being based in ethnically diverse settings. Most studies involved young children and adolescents.[22,23,25-27,33] Young adults have new difficulties and transitions, such as education, careers, intimate relationships and planning families. None of the RCTs in adults with T1DM[30-32] addressed the role of life events and chronic social difficulties on a person's ability to manage his/her diabetes. The majority of studies were grouped based. This may be due to the cost of medical insurance in the US, where most of the studies were conducted. While groups may have the advantage of sharing experiences they do not allow for individualised treatments and may deter patients who are more introverted or who are psychologically distressed.

None of the studies described the method of randomisation or allocation concealment or whether outcome assessors were blind to allocation status. The sample sizes tended to be small. No study described a power calculation or conducted an intention to treat analysis.

2.6 Implications of previous research for proposed study

Sub-optimal control in T1DM is common and associated with increased morbidity and mortality. There have been a broad range of psychological interventions to help people improve their glycaemic control but the quality of these are generally poor and few have used evidence-

based theoretical models. Those studies based on a cognitive behavioural model appear to be most effective. There were no studies which compared brief interventions such as motivational interviewing with longer interventions such as cognitive behaviour therapy. Such comparisons would allow differences in cost effectiveness, applicability in busy clinical settings, patient's resistance to change and patient acceptability to be examined. We propose two interventions based on different theoretical models.

2.7 A motivation model of understanding adherence

Motivational interviewing (MI) is based on a widely used model of health behaviour change which states that two components need to be addressed for sustained behaviour change; first a recognition of the importance of a problem, or conviction that change is needed and second the degree of self-efficacy which reflects confidence in one's ability to bring about a particular behaviour change successfully.[34] In contrast to conventional medical models where the health professional is the expert and the patient the passive recipient of education and advice, MI elicits the patient's concerns as the expert on his difficulties.

MI was originally developed in addictions where its effectiveness has been widely documented.[35-38] It has since been applied to a broad range of health problems, such as eating disorders[39] hypertension in primary care[40] and smokers.[41] There is emerging evidence that it may be effective in improving adherence and glycaemic control in an obese Type 2 female population.[42]

The advantages of MI is that it can be delivered as a brief manual based intervention for a busy clinical setting using computerised tools and non mental health professionals can be trained in its use.[43]

2.8 A cognitive behavioural model of understanding adherence

Cognitive behaviour therapy (CBT) is a pragmatic approach to managing symptoms or illnesses which involves enabling patients to change aspects of their behaviour and the way they think to bring about physiological changes.[44,45] This model is widely used in the treatment of anxiety disorders and referred to as Lang's three systems model[44]. It is based on psycho-physiological evidence that current physiological, behavioural and cognitive responses operate largely in synchrony with one another. Changing one response system such as the person's behaviour will bring about changes in the other two response systems. In diabetes, enabling patients to make cognitive and behavioural changes to their self-care could improve their glycaemic control. For example fears about having a hypoglycaemic attack and perceptions about degree of control over it (cognition) lead to avoiding appropriate diabetes self care (behaviour) which leads to poor diabetic control (physiological).[46] Fearful cognitive responses to previous hypoglycaemic attacks and may be reactivated during times of stress.

While Lang's model focuses on the here and now, Beck's model of emotion, (depression and anxiety), incorporates a developmental perspective. The cognitive theory of emotion stresses that particular biases in information-processing will lead to congruent emotions.[47,48] These biases are reported to be linked to early life experiences which form personal schema, basic attitudes or assumptions and core beliefs. At times of stress, negative thoughts, such as those related to diabetes, might also be activated which then influence coping behaviour. These two models will be used to devise a coherent developmental formulation of the patient's problems which will guide the use of appropriate of cognitive behavioural interventions.

2.9 Summary

Evidence for the effectiveness of psychological interventions to improve diabetes self-care and glycaemic control is poor. We have described two different theoretically based psychological models which have the common goal of improving diabetes self-care. We propose to test the effectiveness of these models in an inner city sample representative of the ethnic and socio-economic diversity of people with T1DM.

3: Research methods

3.1 Hypotheses

Main hypothesis: Motivational Interviewing (MI) plus Cognitive Behaviour Therapy (CBT) will be more effective than usual care at improving glycaemic control in T1DM at 12 months follow up.

Subsidiary hypotheses

(i) Motivational interviewing will be more effective than usual care at improving glycaemic control at 12 months follow up.

(ii) MI plus CBT will be more effective than MI alone at improving glycaemic control at 12 months follow up.

3.2 Design

The design we have chosen is the gold standard for evaluating treatment efficacy; a randomised controlled trial with three arms, MI, MI plus CBT and usual care (see figure 1 – Version 2 dated 18.08.03).

3.3 Setting

Participants from five hospital trusts in South London (King's College, Guy's and St Thomas', Lewisham, Queen Elizabeth (Woolwich) and Mayday) and three hospital trusts in Manchester (North Manchester General Hospital, Manchester Royal Infirmary, Stockport General Hospital) will be recruited. Lambeth Southwark and Lewisham boroughs are one of the most ethnically diverse[49] and socio-economically disadvantaged[50] populations.

3.4 Eligible population

Each diabetes clinic has its own patient database. All current records include patient's age, sex, ethnicity, date of diagnosis, type of diabetes, medication, HbA_{1c} past and present. Each of these databases will be searched to identify patients who have T1DM. Patients who have not had an HbA_{1c} recorded in the previous 12 months will also be included as non-attenders are a vulnerable group.

3.5 Case definition

Diabetes mellitus will be defined according to World Health Organisation criteria.[51] T1DM will be defined: a) onset before age 35 years b) requiring insulin within 6 months from onset and/or c) ketonuria. Sub-optimal glycaemic control will be defined as having at least one HbA_{1c} result between 8.2 and 12% in the previous 12 months. The minimum duration of diabetes will be 2 years to avoid the honeymoon period. We have selected the lower limit of 8.2% as the Diabetes Control and Complications Trial suggests that optimal glycaemic control is a HbA1c of around 7.2% with a significant increase in the risk of complications for every 1% rise in HbA1c above this level.[6] Our upper limit of 12% was selected to exclude a small proportion of patients who are likely to be very physically ill and at risk of being admitted as an emergency. Throughout the study, all measures of HbA1c will be standardised according to the DCCT criteria [6].

3.6 Screening procedure

The diabetes consultants will identify suitable patients and invite them to learn more about the study. Upon on their agreement, the research co-ordinator will contact the patients to discuss the trial in more detail. Interested participants will be sent an appointment with the research co-ordinator at their local hospital to obtain informed consent and then to assess whether the patient meets trial criteria.

3.7 Planned trial criteria

Inclusion criteria: 1) Age 18 to 65; 2) Fluent in English; 3) Not in any other trial 4) A stable dose of antidepressants for 2 months; 5) current HbA_{1c} between 8.2 and 12%.

Exclusion criteria: 1) Pregnancy (if a participant does become pregnant during the study she will remain in the study unless there is a medical contra-indication); 2) Acute/serious medical illness after discussion with the patients physician; 3) severe end stage diabetes complications, that is, registered blind, severe renal disease (creatinine greater than 300 mmol/l); 4) Severe mental disorders; manic-depression, psychotic illnesses, alcohol dependence, learning disability.

3.8 Baseline measures

Socio-demographic: data will be collected on age, sex, level of education, occupation, marital status, self report ethnicity.
Biological: HbA_{1c} (measured at screening); duration of diabetes; complications - retinopathy will be measured by retinal photography;[52] neuropathy will be measured using the vibration-perception threshold[53] and nephropathy will be measured using an early morning urine sample for albumin-creatinine ratio.[54] Body mass index and blood pressure will be measured.
Diabetes specific cognitions: The *Diabetes Specific Health Beliefs-Experience of Treatment and Benefit Barriers* subscale for insulin treated diabetes will be used to measure the patient's perspective of adherence to the diabetes regimen.[55] *Fear of Hypoglycaemia* questionnaire[46] will be used as worries are not adequately measured by the *Diabetes Specific Health Beliefs*. The *Beliefs about Medicine Questionnaire* will be used to elicit beliefs about the use of insulin.[67]
Diabetes specific behaviour: The *Summary of Diabetes Self –Care Activities* questionnaire measures frequency of adherence to eating habits, exercise levels, glucose monitoring and medication.[56]
Psychiatric morbidity: This will be measured using the *Primary Care Evaluation of Mental Disorders (PRIME-MD PHQ)*[57] which is a self report measure for depressive, anxiety, alcohol, somatoform and eating disorders and using the *General Health Questionnaire-12.*[68] The *Life Events Questionnaire* [69] will be used to determine perceived stress and the World Health Organisation's *Alcohol Use Disorders Identification Test* to measure alcohol consumption. [70]
Quality of life: The *Short Form-36* [58] will be used which has been used extensively in diabetes. The *EuroQOL*[71] will be used in order to conduct a cost-utility analysis, and the *Diabetes Quality of Life* measure to look at diabetes-specific themes. [72]
Costs: *Client Services Receipt Inventory*[59] gives a detailed description of service use patterns, medication (including insulin), employment and household family responsibilities in the previous 3 months.
Social support: from family, friends and health professionals will be examined by the *Significant Others Scale.*[66]

3.9 Randomisation procedure

Before randomisation all participants will receive a 2 page fact sheet on Type 1 diabetes to ensure that the minimum acceptable level of diabetes education is equal in all three groups (see fact-sheet version 1 – 18.08.03). Randomisation will be conducted by the Clinical Trials Unit (CTU) at the Institute of Psychiatry who will prepare a randomisation list using permuted blocks of random sizes to ensure an equal number of patients in each group while avoiding possible predictability associated with blocks of fixed sizes. Allocation concealment will be ensured by the randomisation list being held by the CTU who will use a program that reveals the allocations only when the patient identification number is entered.

3.10 Planned health technologies

Technology 1: Motivational interviewing

The main objective of MI will be to bring about changes in behaviour by enhancing motivation. Patients allocated to the MI group will receive 4 individual sessions lasting one hourevery fortnight for 2 months. A computerised assessment will be carried out using the Accu-Chek interview [60] developed for use by patients with diabetes. This tool incorporates key MI tasks; a menu of self care behaviour change options; assessment of importance and confidence of change in a self care topic selected by the patient; and the identification of specific patient barriers that influence patient confidence around behaviour change. Work in the US and our pilot suggests it has face validity for patients [61]. The advantages of a computerised assessment tool is that it increases motivation, self-efficacy and behaviour change. [62]At the first session the computer assessment will be conducted. The patient will select one self care topic from 7 options: self-monitoring of blood glucose, food and eating, exercise, hypoglycaemia, smoking, a topic provided by the patient and a "no topic today" option. The software generates a 1-page report for the patient that summarise the self-care topic identified by the patient. It also gives ratings of importance and confidence regarding

behavioural change and barriers to change in the topic identified by the patient. Following the Accu-Chek the patient and nurse will discuss the topic selected, exploring importance of change and building confidence regarding change.

Motivational interviewing techniques include non-challenging, non-judgmental and reflective communication, clarifying problems and advantages, information gathering and presenting options. Potential solutions to each barrier identified by the patient will be discussed as well as potential benefits from improvement in self-care. The discussion is then summarised and a specific action plan negotiated. The next three sessions will review the discussion and action plans from the previous session and then cover the topic selected on the day for discussion by the patient.

Technology 2: Motivational Interviewing plus Cognitive Behavioural Therapy

Participants will receive 4 sessions of MI as described above followed by 8 sessions of CBT. The main objective of CBT will be to enable the patient to identify and modify unhelpful diabetes specific cognitions and behaviours which may be contributing to poor glycaemic control. Eight individual sessions lasting one hour each over a 4-month period will be given. Treatment will be individualised, conducted collaboratively and follow a modified version of Kanfer and Schefft[63] seven phases of treatment: Phase 1 – assessment (behavioural analysis, life history, role of significant others, perception of diabetes); Phase 2 - establishing a therapeutic alliance; Phase 3 – generating the willingness to change; Phase 4 - giving the patient a rationale for treatment; Phase 5 - conducting the treatment; Phase 6 - monitoring and evaluating progress; Phase 7 - generalising the progress and ending treatment.

Each treatment session is structured. At the start of every session an agenda is agreed, which is patient led and guided by the therapist. This is to ensure that all issues are addressed within the time available. Sessions usually last up to one hour. Homework which takes the form of specific behavioural and cognitive goals which have previously been agreed are discussed. Success with homework and problems are discussed. New homework is negotiated and agreed. At the end of each session key points discussed are summarised. The nurse therapist always keeps in mind the end of treatment targets which have previously been agreed as these are to be worked towards systematically.

Techniques used will be tailored to the individual needs of the patient. A rationale will be given for those cognitive and behavioural changes which the patient and therapist has agreed upon. Interventions will include: involving significant others; normalising dietary, exercise and life style related behaviours; anxiety, worry and stress management; challenging negative automatic thoughts (anxiety or depression related); improving impulse control; behavioural experiments; activity scheduling; strategies for eliciting social support; assertiveness training.

Control group

Patients randomised to the control group, and the groups receiving MI and MI plus CBT, will have their usual diabetes care. The participating centres have agreed to a protocol of minimum acceptable diabetes care which is an annual review modelled on the protocol recommended by the Diabetes National Service Framework. All centres agree to the same aims of diabetes treatment of a HbA1c $\leq$ 7.0% with no problematic hypoglycaemia (see Protocol for usual care: version 1 18.08.03)

3.11 Delivery of technologies It is important that both technologies are clearly defined and described to enable subsequent replication and use by other health professionals. Both technologies will be delivered by diabetes specialist nurses (DSN) and this will be achieved by several means:

1. The psychologist will pilot MI and CBT with supervision from TC, US, JT and KI. A protocol for supervision will be agreed upon.
2. A training manual will be written by the psychologist to ensure standardised training of diabetes nurse specialists in both MI and CBT. We will integrate training manuals for MI with in house and internet based training manual in MI.[64]
3. A measure for assessing a set of competencies and skills will be used during training and throughout the trial.[65]

4. Patients who will receive MI and/or CBT for the purposes of training the nurses only will be given a separate patient information sheet explaining the technologies and that the nurses are in training and their written consent will be required before they start (see patient information sheet and consent form for training version 1).
5 A treatment manual for use by the DSN will be written for both MI and CBT by the psychologist under the guidance of TC and UC. The manual will include a section on diabetes management as suggested by the patients in the focus group.
6. Audio-taping of all treatment sessions will be carried out and a random sample will be rated by the supervisor and an independent assessor blind to allocation.
7. The psychologist will give weekly group and individual supervision to the DSNs.
8. Patients in the MI group will receive their Accu-check print out of the problems they have identified. Patients in the CBT group will receive a series of information sheets, given at the end of each session, titled 'Living with Diabetes'. These will cover the CBT model and common problems encountered by people with diabetes.
9. The investigators will meet with the research team regularly to ensure the trial is running according to plan.

3.12 Outcome

Main outcome: this will be the glycaemic control, measured by HbA_{1c} at 12 months follow up. However, we will also check patients HbA_{1c} at 3, 6 and 9 months to measure whether improvement is stepwise, gradual or sustained.

Subsidiary outcomes at 12 months follow up to measure change:

1. Biological: diabetes complications status will be repeated if not done 3 months before or after end of 12 month follow up at annual diabetes review. Body mass index and blood pressure will be measured.

2. Diabetes specific cognitions: The *Diabetes Specific Health Beliefs-Experience of Treatment and Benefit Barriers*; *Fear of Hypoglycaemia* questionnaire; and *Beliefs about Medicine Questionnaire*.

3. Diabetes specific behaviour: The *Summary of Diabetes Self –Care Activities.*.

4. Psychiatric morbidity: *Primary Care Evaluation of Mental Disorders (PRIME-MD PHQ); GHQ-12*; the *Alcohol Use Disorders Identification Test and the Life Events questionnaire.*

5. Quality of life: The *Short Form-36*; the *EuroQOL*; and the *DQOL*.

6. Costs: *Client Services Receipt Inventory*

7. Social support: from family, friends and health professionals will be examined by the *Significant Others Scale*.

8. Adverse events checklist. A list of adverse events if and when they are reported will be compiled. Potential adverse events presently identified include any death, psychiatric admission, medical admission, onset of complication secondary to rapid glycaemic control (painful neuropathy, accelerated retinopathy, hypoglycaemic episodes).

3.13 Measures of process

At three monthly intervals insulin regime will be recorded in order to measure the total dose of insulin.

At 6 months from baseline, social support will be measured with the *Significant Other Scale* [66] to assess how it mediates the effect of health technologies on glycaemic control.

3.14 Ethical arrangements

Risks and anticipated benefits: CBT and MI are extremely safe interventions with negligible risks for the trial participant and for society. If either technology was effective, this could improve the care that patients with T1DM receive safely and with little extra cost to the NHS. Informing potential participants: psychological interventions are safe. Consent: All patients will be asked to give written informed consent.They will be given a brief summary of the current evidence for psychological interventions in diabetes and the rationale behind randomisation. All patients will be given a copy of their signed consent form and information sheet and one will be filed in the medical notes. Confidentiality: The database that contains the patients' names addresses and unique identifier will be accessed only by the research co-ordinator and the principal investigator. All other

data will be stored separately where patients will be identified by their unique identifier. Time period: retention of trial documentation is estimated at ten years.

3.15 Proposed sample size

We will assume that the baseline HbA_{1c} is approximately 9.0% [6]. We will assume that the post CBT or post MI mean will be 8% based on the evidence that a reduction of 1% in HbA_{1c} is associated with a clinically and statistically significant reduction in risk of developing diabetes complications.[6] We will assume that control mean HbA_{1c} will be 8.8% (based on the principle that participating in the study as a control can have a slight improvement on glycaemic control.[6] We further assume that the standard deviation of the changes is approximately equal to 1.65 based on the average standard deviation of the change scores in a RCT of cognitive analytic therapy at 3 month follow up from end of intervention period.[31] We therefore require 90 subjects per group to achieve 90% power to detect the difference in mean change between two groups using a t-test with a 5% level of significance. Allowing for a 20% drop-out rate, we therefore need 113 subjects for each arm giving a total of 339 participants.

3.16 Statistical analysis

Data will be entered using SPSS and analysed using STATA. The success of randomisation will be assessed by comparing baseline characteristics. The difference in mean reduction of HbA_{1c} between the CBT, MI and control groups will be estimated using a linear mixed model incorporating fixed effects of group, time and group by time and a random effect for subjects. All available data will contribute to the analysis including data on subjects who dropped out or withdrew from the trial (intention to treat analysis). The same analysis will be used to identify other predictors, such as presence of diabetes complications and psychiatric morbidity and effect modifiers such as social support. Secondary outcomes (illness perceptions and diabetes specific behaviours) will be analysed using linear mixed models and generalised linear mixed models for dichotomous outcomes. We will model the change in mean HbA1c over time using a linear trend and a quadratic one if needed. The change over time is reflected by the linear trend, "the effect of time", and a treatment effect would correspond to a group by time interaction. A comparison of participants and non-participants of the RCT will be performed on socio-demographic data available from the databases. A comparison of the baseline characteristics of completers and non completers will be done. Economic analysis: Total average costs will be linked with the main outcome (improvement in HbA_{1c}) for each group in the form of a cost-effectiveness analysis. A cost-utility analysis will be conducted on the *SF-36*. This will offer a simpler decision rule and allow explorations of cost per quality-adjusted life-year (QALY) gained.

3.17 Independent supervision of trial

Trial steering committee (TSC): The following have agreed to form the TSC; Professor Glyn Lewis (Chair), Professor of Psychiatry, Bristol University Department of Psychiatry, Manchester Royal Infirmary; Dr Bianca De Stavola, Senior Lecturer in Medical Statistics, London School of Hygiene and Tropical Medicine and Dr Dennis Barnes, Consultant Diabetologist, Kent and Sussex Hospitals, Tunbridge Wells. **Data monitoring and ethics committee (DMEC):** the following have agreed form the DMEC; Professor Graham Dunn (Chair), Professor of Medical Statistics, Department of Epidemiology and Health Sciences, University of Manchester; Professor Robert Peveler, Department of Psychiatry, University of Southampton; Dr Peter Watkins, Honorary Consultant Physician, King's College Hospital. Meetings will be arranged by the research co-ordinator and held at the Host Institution. Observers from HTA and Professor Simon Wessely (Host institution observer) will be invited to all meetings. The committees will convene separately at least twice a year to advice, comment and supervise the research team.

3.18 Pilot work

Target population. The diabetes databases at the three hospitals were screened to identify the size of the target population. Nearly all patients with Type 1 diabetes in LSL will be registered with at least one of the three hospital. We identified that the number of current patients in LSL at King's College, Guy's and St Thomas' and Lewisham Hospitals with a HbA1c of >8.2% was 322, 208 and 94 patients (n=624) which is more than ample to fulfil our sample size requirements.

Users. We organised a Focus group to discuss the trial and potential interventions. Users from the South London branch of Diabetes UK (Ms Janet Keys) and patients who had attended 'DAFNE' group sessions (Ms Helen Reid, Diabetes Centre, King's College Hospital) were invited to attend a group to describe CBT and MI to them and for their feedback. The group (n=12) was very heterogeneous. They highlighted the following; need for individualised plans, difficulties communicating their concerns to the diabetes team, a preference for fortnightly sessions, the need for a revision course in diabetes management. They welcomed our proposal as timely and some individuals volunteered to give feedback on information leaflets.

Motivational interviewing. We have piloted the MI technology with 15 patients with T1DM and eating disorders. The interview techniques were acceptable to patients, especially those early in their history of eating problems. Patients found the Accu-Check computerised assessment helped to focus on their perceived problems. HbA_{1c} before and after MI was taken for 5 patients. Paired t-test revealed a clinically significant improvement in HbA1c of 12.7 (SD 2.6) versus 11.6 (SD 2.9), p=0.07. These preliminary results are encouraging as they suggest that MI appears to be effective in people with complex problems.

CBT: Over 20 patients from the Diabetes Centre Liaison Clinic have been referred for CBT delivered by a trained nurse specialist at King's College Hospital. The nurse therapist has assessed and treated over 20 patients with T1DM and we have identified common themes about having diabetes: stigma, self-consciousness, hectic multiple social roles, fear of fatness, depression, binge eating, anger, denial, difficulties communicating with doctor. Using these themes, our techniques have been further developed and revised.

3.19 Dissemination

We will use formal and informal methods for dissemination. We will submit papers using CONSORT criteria to leading journals such as the Lancet, BMJ and main diabetes journals. We will present our findings at diabetes, psychology and liaison psychiatry conferences. A full report with the executive summary will be sent to all NHS authorities to assist in dialogues about improving diabetes care nationally. We will develop a website for our study and findings. We will liase with Diabetes UK and hold meetings with local users groups and collaborate with Royal College of Physicians, Psychiatrists and Nursing on future recommendations for psychological care for people with T1DM.

4 PROJECT TIMETABLE AND MILESTONES

Months 1 to 6. Write manuals. Train one DSN in MI and 2 DSNs in CBT. Research co-ordinator identifies target population for screening and randomisation. Months 7-30 delivery of technologies, inter-rater reliability, follow ups, independent ratings, data entry. Months 31-36 data entry, analysis, preparation for publication, study report and dissemination. We estimate that the recruitment rate will be between 5 to 10 patients a week during months 7 to 18.

Project milestones	01-03	04-06	07-09	10-12	13-15	16-18	19-21	22-24	25-27	28-30	31-33	34-36
Training psychologist	*	*										
Preparation of manuals	*	*										
Training DSNs in MI and CBT	*	*										
Recruitment			*	*	*	*						
Identify target population & sample		*										
Delivery of technologies			*	*	*	*	*	*				
Follow up (HbA_{1c}): 3,6,9 &12 mths				*	*	*	*	*	*	*		
Supervision	*	*	*	*	*	*	*	*	*	*		
Data entry			*	*	*	*	*	*	*	*	*	
Analysis and preparing manuscripts											*	*
TSE & DMEC meetings	*	*			*						*	

5 EXPERTISE

We have established an experienced multidisciplinary multi-centre consultation team for this proposal to ensure that medical, psychological, epidemiological, statistical and economic dimensions are fully addressed:

Khalida Ismail is a Liaison Psychiatrist and an Epidemiologist. She has over 4 years experience of running a liaison psychiatry clinic with nurse CBT therapist in Diabetes Centre, King's College Hospital. She has worked with her co-applicant (TC) in developing a CBT model. She has had extensive experience in conducting epidemiological studies on medically unexplained symptoms and psychiatric aspects of diabetes, which include a Wellcome Trust project on depression and foot ulcers and a Cochrane review of psychological interventions in diabetes.

Trudie Chalder is a Reader in the Department of Psychological Medicine. Originally dual trained in nursing, she is a qualified behavioural psychotherapist. Her expertise is in cognitive behavioural models of chronic ill health. She devised a model for understanding chronic fatigue syndrome. She has conducted 5 RCTs testing the efficacy of CBT interventions in various clinical settings including a HTA funded RCT of CBT for irritable bowel syndrome where nurses were trained as advocated in this proposal. She has extensive experience in training CBT techniques and supervision. She has developed a cognitive behavioural model of understanding adherence difficulties with diabetes self care in people with T1DM.

Janet Treasure is Professor of Psychiatry, St Thomas's Hospital and has specialised in the treatment of eating disorders including diabetes for over twenty years. She is Director of the Eating Disorder Unit at the South London & Maudsley Hospital NHS Trust. She has run group therapy sessions for T1DM patients; developed a self help handbook on eating problems in diabetes 'You and your diabetes' and piloted the technique of motivational interviewing. She is a trainer in motivational interviewing. She has expertise in co-ordinating pan European multi-centre studies of the aetiology of eating disorders. She has edited two texts on eating disorders, authored 2 self help books and co-ordinated three RCTs of CBT and MI for eating disorders.

Ulrike Schmidt is Senior Lecturer and Consultant Psychiatrist in Eating Disorders at the Institute of Psychiatry. She is a recognised trainer in Motivational Interviewing. She has extensive experience in working with diabetic patients through her previous work as a liaison psychiatrist at St. Mary's Hospital and her current work in eating disorders, where she has piloted the use of motivational interviewing techniques in obese Type 2 patients. She has extensive experience in designing and conducting motivational interviewing and brief CBT RCTs in eating disorders and liaison psychiatric populations. She has expertise in preparing self-help and clinician manuals. She is currently evaluating brief computerised psychological interventions

Sophia Rabe-Hesketh is a Senior Lecturer in Statistics at the department of Biostatistics and Computing. She has seven years experience as a statistical consultant and has been project statistician for numerous clinical trials. She has co-authored three textbooks in statistics and over thirty papers in both medical and statistical journals.

Anita Patel is a qualified health economist at the Centre for the Economics of Mental Health (CEMH) at the Institute of Psychiatry. She is currently working on 6 NHS and MRC funded RCTs with substantial health economics components. She also has experience of investigating other chronic conditions such as stroke and asthma. Ms Patel is also able to draw upon the skills of colleagues at CEMH, particularly her supervisor Professor Martin Knapp (Professor of Health Economics and Director of CEMH), who is an international expert in the economics of psychological treatments.

Stephen Thomas is a Consultant Physician and Honorary Senior Lecturer in Diabetes at King's College Hospital. He was formerly a Lecturer at Guys and St Thomas's Hospital and his close links there will contribute to the smooth running of the study. He has had extensive research experience in epidemiological, intervention and biological studies of diabetes complications and his clinical expertise in diabetes should ensure that the medical aspects of patients care is supervised adequately and that non psychological factors are being examined rigorously.

Richard Jones is a Senior Lecturer in Diabetes based St Thomas's Hospital. He has had over 30 years of clinical experience of diabetes, especially T1DM, and is a leading expert on insulin therapies. He is an expert in community diabetes management.

Collaborators Dr Andrew Worsley, Consultant Diabetologist, Lewisham Hospital will facilitate recruiting from Lewisham Hospital. Dr Garry Welch, Joslin Diabetes Center, Harvard Medical School, Boston, US will provide additional supervision on the Accu –check.

6 JUSTIFICATION OF SUPPORT REQUIRED

6.1 Nurses

Three fulltime G grade DSNs will be needed over a two and half year period to delivery the technologies; 2 nurses for CBT and 1 for MI. This would cover a 6 month training period, 12 months recruitment and 12 months of follow up. They will need training, administrative time, deliver the technology, writing up sessions, and time for individual and group supervision, booster training sessions and data entry. If either technology is beneficial we will have determined that DSNs can deliver them. DSN are the most appropriate non medical professional as they can combine their expert knowledge of diabetes with our proposed psychological skills. Clinical psychologists are scarce and more expensive.

6.2 Clinical psychologist

A psychologist is required to refine the treatment manuals, devise and implement the training of the nurses, prepare a training manual and conduct ongoing supervision. In addition the psychologist will carry out the baseline psychiatric assessments.

6.3 Research coordinator

A research worker with training in epidemiology will be required to co-ordinate the study. He/she will liase with diabetes consultants to identify and contact the patients, liaise with all members of the research team, data collection and entry, conduct blind assessment at baseline, 6 months and 12 months follow up. He/she will organise meetings with the TSC and DMEC. The co-ordinator will be expected to enrol for a PhD studentship at GKT School of Medicine.

6.4 Health Economist

Anita Patel will be responsible for conducting the economic analyses. She will adapt the CSRI for use in this study, collate/estimate unit costs, set up the economic database/coding frame, conduct the economic analyses using already computerised data and write up results of the economic evaluation for the study report and publication.

6.5 Independent psychologists

Two independent psychologists will be required on a sessional basis to rate a random sample of therapy sessions.

6.6 Adverts

This is to cover the cost of advertising the research posts.

6.7 Equipment

We will require three sets of audio-equipment and tapes to record all therapy sessions for supervision and subsequent rating for treatment fidelity (1,540 sessions). We will need 3 desktop and 3 laptop computers and 1 colour printer and 2 basic printers. One answering machine is required for patients and staff to leave messages. Word processing, desktop publishing and statistical software will be required.

6.8 Conference

Conferences are increasingly expensive but are a necessary means of learning, collaborating and gaining feedback. The relevant conferences will include the Diabetes UK, American Diabetes Association, psychiatry and psychology conferences. We have estimated the cost of attending six international or national conferences in three years.

6.9 Travel expenses

We have calculated travel on the basis of the cost of a Zone 1 and 2 day travelcard for participants per session in all three arms of the study. We have also included travelcards for the research co-ordinator, clinical psychologist and the nurse specialists to attend training and supervision sessions. Travel costs for members of the Trial Steering Committee and Data Monitoring and Ethics Committee to meet in London twice a year for three years.

6.10 Lab costs

We will need to carry out HbA1c at baseline on the eligible population and four subsequent follow-ups at 3, 6, 9 and 12 and 18 months which amounts to approximately 1,530 blood tests at £4 each.

6.11 Stationary

The study will generated a considerable amount of print, including patient leaflets, information sheets, questionnaires, coding booklets, training manuals, letters, appointments, diaries and homework sheets. Files and wallets will be needed to ensure confidential storage of data and stamps will be required for posting of correspondence and appointments.

6.12 PhD fees

We envisage that the research co-ordinator will carry out a PhD.

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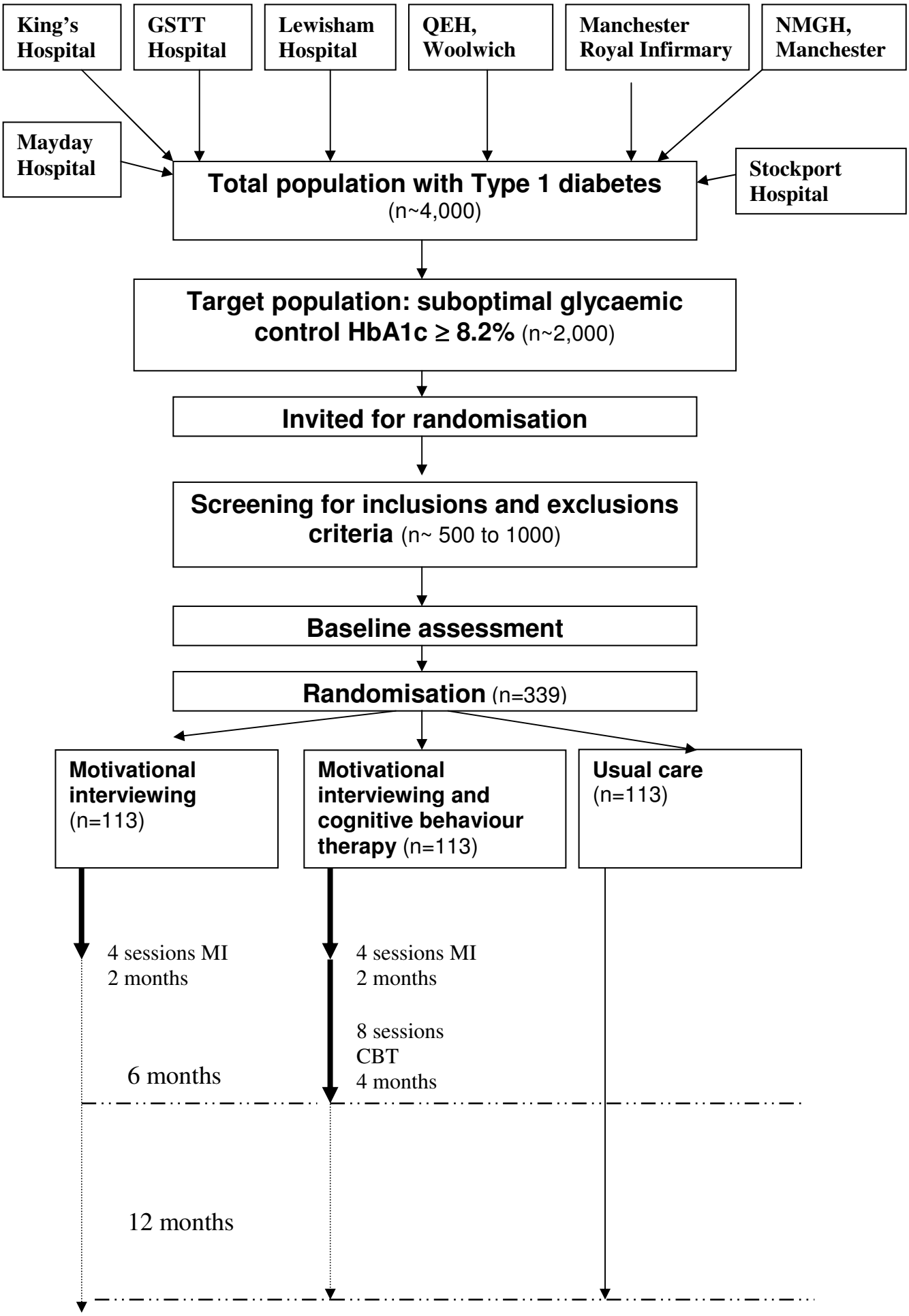
Figure 1. Study design – version 2, 18.08.03



Appendix for ADaPT study protocol (dated 18.08.03)

1. Case definition (section 3.5, p 4) and Inclusion criteria (section 3.7, p 4)

The HbA1c range has been changed from 8.2-12% to 8.2- 15%.
The rationale is that these patients are not necessarily acutely medically ill and are potentially just as likely to benefit from psychological treatment.
DMEC has approved of change (minutes 03/02/04).

2. Trial statistician (section 5, p 10)

Sophia Rabe-Hesketh has been replaced by Polly Hardy, who is a Lecturer in Medical Statistics at the LSHTM. She joined the team in May 2004. Polly Hardy has now been replaced by Jonathan Bartlett also based at the LSHTM (please see relevant section in HTA reports and updates)

3. REVISED PROJECT MANAGEMENT PLAN (section 4, p 9)

Table 1 describes the revised project plan to take account of the additional 9 months extension, recruiting of new staff, training new staff, extension in the delivery of technologies and delay in completing data entry and writing up.

Table 1: revised project milestones in 3 monthly periods

Milestones	01-03	04-06	07-09	10-12	13-15	16-18	19-21	22-24	25-27	28-30	31-33	34-36	37-39	40-42	43-45
Training psychologist	●	●													
Preparation of manuals	●	●													
Training DSNs in MI and CBT	●	●					*								
Recruitment of patients			●	●	●	●	*	*	*	*					
Identify target population & sample		●													
Delivery of technologies			●	●	●	●	●	●	*	*	*	*			
Follow up (HbA_{1c}): 3,6,9 &12 mths				●	●	●	●	●	●	●	*	*	*	*	
Supervision	●	●	●	●	●	●	●	●	●	●	*	*			
Data entry			●	●	●	●	●	●	●	●	●	*	*	*	*
Analysis and preparing manuscripts											●	●		*	*
TSC & DMEC meetings	●	●			●						●				
Recruitment of research nurses					*	*									

●= original milestones *= revised milestones