Sheffield Health and Social Care NHS Foundation Trust

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STEPWISE: STructured lifestyle Education for People WIth SchizophrEnia

(including schizoaffective disorder and first episode psychosis)

Intervention Development Study to adapt the DESMOND™ programme to people with Schizophrenia, schizoaffective and first episode psychosis; and,

a multi-centre randomised controlled trial assessing STructured lifestyle Education for People WIth SchizophrEnia (including schizoaffective disorder and first episode psychosis) to reduce weight gain of patients prescribed antipsychotic medication.

RESEARCH PROTOCOL
Version 9.0; 9 May 2016

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Sponsor: CSP 138897
NIHR HTA: 12/28/05
ISRCTN: 19447796
Sheffield CTRU: R/ 134498
NRES REC: 14/YH/0019

STructured lifestyle Education for People WIth SchizophrEnia (including schizoaffective disorder and first episode psychosis)

This document describes the STEPWISE research project. The project includes an Intervention Development Study (IDS) which will adapt the DESMOND™ Let's Prevent programme to meet the needs of people with Schizophrenia; and, a randomised controlled trial. For the purposes of the project, schizophrenia is defined by ICD-10 codes F20 (schizophrenia) and F25 (schizoaffective disorder) and will include people with first episode psychosis (defined as having started taking antipsychotic medication less than 3 years ago). The document provides information about procedures for entering participants. The protocol is not intended for use as a guide to the treatment of other patients. Amendments may be necessary; these will be circulated to participants in the trial (as appropriate).

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Abbreviations

AE	Adverse event
CI	Chief Investigator
CONSORT	Consolidated standards of reporting trials
CRF	Case report form
CTRU	Clinical trials research unit
CMHT	Community Mental Health Team
DESMOND	Diabetes Education and Self Management for Ongoing and Newly Diagnosed
DMEC	Data Monitoring and Ethics Committee
GCP	Good Clinical Practice
GEE	Generalised estimating equation (model)
GP	General Practitioner
HRQoL	Health related quality of life
HTA	Health Technology Assessment
ICD-10	International Classification of Diseases (10^{th} revision)
IDS	Intervention Development Study
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health Research
NHS	National Health Service
NPT	Normalization Process Theory
PI	Principal Investigator
QALY	Quality adjusted life year
R&D	Research and Development
RCT	Randomised control trial
REC	Research ethics committee
SAE	Serious adverse event
ScHARR	School of health and related research
SOP	Standard operating procedure
SHSC	Sheffield Health and Social Care (NHS Foundation Trust)
TDF	Theoretical Domains Framework
TMG	Trial Management Group
TSC	Trial Steering Committee

Project details

The research intervention will be developed by the DESMOND Collaborative, University Hospitals of Leicester NHS Foundation Trust, based on the existing NICE approved structured education programme for patients with, or at risk of, type 2 diabetes. A full list of co-investigators is available on the study webpage: www.shef.ac.uk/scharr/sections/dts/ctru/stepwise.

The project is funded by the National Institute for Health Research (NIHR) Health Technology Assessment (HTA) Programme.

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Protocol amendments

Version number	Change/s made	Date of REC approval*	Amendment number
2.0	Change to calculation of the primary outcome. Revised sample size. Clarification of eligibility criteria; description of the control arm and qualitative research component.	21 August 2014	1.0 (substantial)
2.1	Change to allow additional centres and iterations, if required, for the IDS. Added reference to use of weight loss programmes (outcome), and schizoaffective disorder approved as part of the previous amendment.	5 November 2014	2.0 (non-substantial)
3.0	Change to: screening and consent process to ensure recruitment closer to scheduled intervention sessions; SAE reporting; updated project plan; and other minor changes.	23 December 2014	2.0 (substantial)
4.0	Removed provision for participants to be accompanied to intervention sessions during the RCT (IDS recommendation). Clarified processes for taking fasting blood sample, and completing OPCRIT+. Added details about referring any concerns/risk to the clinical care team.	18 March 2015	3.0 (substantial)
4.1	Change to clarify the procedure for collection of baseline accelerometry data and fasting blood sample. Data collection may occur after randomisation due to the group nature of the intervention and need to consent as close to scheduled education courses as possible.	9 April 2015	3.0 (non- substantial)
5.0	Change to: increase data collection windows for OPCRIT and outcome assessment; clarify: data collection for intervention attendance and sharing blood test results; addition of STEPWISE curriculum plus format corrections.	24 June 2015	4.0 (substantial)

Version number	Change/s made	Date of REC approval*	Amendment number
6.0	Changes to: clarify 'community mental health teams' includes a range of services and can include patients stepping down from inpatient to community services if they can fully implement the learning from the intervention; allow an additional week for collection of fasting blood sample at 12 month follow-up (in line with changes to v4.0 - bloods and v5.0 - follow-up windows); and that most qualitative interviews will be conducted by telephone. Minor corrections in line with previously agreed changes, site staff changes; and, CTRU SOP PM004.	25 November 2015	5.0 (substantial)
8.0	Changes to: indicate that over-recruitment is anticipated (up to maximum 50) due to the need for centres to recruit in waves and run a (intervention) group with sufficient participants; clarify that unrelated contact with mental health services is not counted when defining first episode psychosis; and, clarify that the analysis will include whether the intervention has the same effect among recently diagnosed patients as it does among those established on anti-psychotic medication for a greater period of time. Minor errors (e.g. (typographical) also corrected.	24 February 2016	6.0 (substantial)
9.0	Change to include invitation to be contacted about further research at the participant's 12 month follow-up visit.	2 June 2016	7.0 (substantial)

*For non-substantial amendments the date relates to notice of acknowledgement.

Project Summary

Intervention Development Study
The intervention development study will adapt the NICE approved education programme DESMOND™, to meet the needs of people with schizophrenia, schizoaffective disorder or first episode psychosis. Originally designed for people with or at risk of diabetes the programme has already been adapted for use in minority ethnic groups and people with learning disabilities to help people to change their lifestyle by eating more healthily and exercising more.

The IDS will be conducted through four phases: (1) systematic review & evidence synthesis, (2) qualitative data collection, (3) programme development (4) programme pilot & refinement.

The IDS will recruit approximately 15 patients during stage 4 and deliver a test intervention in 2-3 iterative cycles. Further cycles may be completed as required. Focus groups and semi-structured interviews will capture participants' feedback on the intervention. Once developed, the lifestyle programme will be tested in a randomised controlled trial in the target population compared with usual care (control).

Randomised Controlled Trial

DESIGN: A multicentre open-labelled individually randomised (parallel group) randomised controlled trial of a group lifestyle education programme in people with schizophrenia including those with first episode psychosis.

SETTING: A variety of different community mental health locations, in 10 UK Mental Health Trusts, that are convenient and familiar to participants including hospitals and primary care or community venues.

TARGET POPULATION: Adults with schizophrenia, schizoaffective disorder or first episode. Views of mental healthcare professionals will also be sought to assess the acceptability of the intervention.

RECRUITMENT: Clinics and other community services run by the Mental Health Trusts with a 12 month recruitment period at each site.

INTERVENTION: An adapted DESMOND™ programme delivered to a group of approximately 6-8 people in 4 weekly ~2.5 hour session by two trained facilitators, with modules (such as, the patient story, physical activity, and diet) designed to target perceptions and knowledge of risk status and chronic disease, self-efficacy and response-efficacy beliefs around health behaviour. Support contact and booster sessions provided by facilitators.

FEASIBILITY: An assessment of study feasibility will be made based on four conditions at 24 months: 1) fewer than six centres have recruited their first participant; 2) fewer than 125 participants have been consented; 3) fewer than three centres have completed their first four-week STEPWISE course; 4) fewer than 75% of those followed up to their three month outcome assessment have contributed valid weight (primary outcome at 12m) data at this time point.

MEASUREMENT OF OUTCOMES: Primary outcome: weight (kg) change at 1 year post-randomisation. Secondary outcomes: 1) weight (kg); proportion who maintained or reduced weight; % weight change; 2) waist circumference; 3) body mass index; 4) Wrist worn accelerometry (GENEActiv); 5) Adapted Dietary Inventory Nutrition Education questionnaire; 6) Blood pressure; 7) Fasting glucose, lipid profile, HbA_{1c} (baseline & 1 year only); 8) Health-related quality of life (EQ-5D & RAND SF36); 9) Brief Illness Perception Questionnaire (adapted B-IPQ); 10) Brief Psychiatric Rating Scale; 11) Client Service Receipt Inventory (including changes in medication; 12) Smoking status; 13) Adverse events; 14) Patient

Health Questionnaire 9 (PHQ-9); 15) use of weight loss programmes; 16) Session Feedback (intervention only).

DURATION OF FOLLOW UP: The primary analysis will be undertaken at 12 months after randomisation. All secondary outcome measures will be assessed at baseline and after 3 and 12 months except where stated.

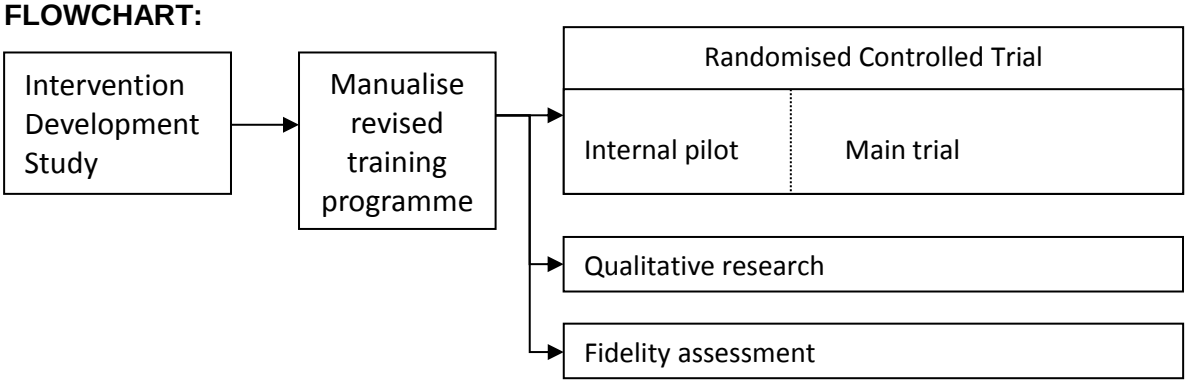
TRIAL SAMPLE SIZE: A sample size of 198 patients for each trial arm (396 in total), stratified by centre and duration of illness, to ensure the primary outcome (12 months weight change) achieves a 95% power to detect a minimum clinically important difference of 4.5 kg using a two sided significance level of 5%. This figure is based on previous data where the mean weight at baseline is approximately 90 kg, assumes a conservative standard deviation of 10kg, takes into account within-course clustering in the intervention arm (ICC=5%; average group size 7), and an anticipated dropout of 20%.

PLANNED ANALYSES: The analysis will be performed on an intention to treat basis and all statistical tests will be two-tailed at 5% significance level. Socio-demographic characteristics of participants at baseline will be summarised and assessed for comparability between the intervention and control arms. The primary outcome will be assessed using a marginal generalised estimating equation model (GEE). An adjusted analysis will be performed which will include baseline covariates and any observed imbalances. Secondary continuous outcomes will be analysed in the same manner as the primary outcome. For binary outcomes analysis will be undertaken using a marginal generalised logistic linear regression model within the GEE framework and difference between treatment groups will be reported as Odds Ratios.

QUALITATIVE SUB-STUDY: The sub-study will invite 20-24 participants in the intervention arm to take part in a semi-structured interview. The study will explore patients' views about recruitment, acceptability and satisfaction with the research protocol, and satisfaction with the lifestyle education programme. Approximately 20 facilitators will also be invited to take part in a semi-structured interview. A fidelity assessment of the intervention will also be carried out.

PROJECT TIMETABLE (planned): Months 1-12: adaptation of DESMOND™ and all essential documentation, convene the Trial Steering Committee, obtain REC approval & commence contracting; Months 12-14: site set-up (n=10) starts; Month 13 onwards: revised training course will be available; Months 15 – 30 staggered centre initiation and recruitment; Month 42: last participant followed up; Month 42-48 closedown, analysis and write-up.

FLOWCHART:



PROJECT PLAN:

	STEPWISE: STructured lifestyle Education for People WIth SchizophrEnia	Oct-13	Nov-13	Dec-13	Jan-14	Feb-14	Mar-14	Apr-14	May-14	Jun-14	Jul-14	Aug-14	Sep-14	Oct-14	Nov-14	Dec-14	Jan-15	Feb-15	Mar-15	Apr-15	May-15	Jun-15	Jul-15	Aug-15	Sep-15	Oct-15	Nov-15	Dec-15	Jan-16	Feb-16	Mar-16	Apr-16	May-16	Jun-16	Jul-16	Aug-16	Sep-16	Oct-16	Nov-16	Dec-16	Jan-17	Feb-17	Mar-17	Apr-17	May-17	Jun-17	Jul-17	Aug-17	Sep-17
#	**Month**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**	**25**	**26**	**27**	**28**	**29**	**30**	**31**	**32**	**33**	**34**	**35**	**36**	**37**	**38**	**39**	**40**	**41**	**42**	**43**	**44**	**45**	**46**	**47**	**48**
1	Contract with Funder	1																																															
2	Sponsor contract with CRO	1	2																																														
	INTERVENTION DEVELOPMENT STUDY (IDS) AND ROLL OUT																																																
3	Literature review	1	2	3	4																																												
4	DESMOND team make prototype *(protocol development)*	1	2	3	4	5	6																																										
5	Participating trusts identify 3-4 educators					1	2																																										
6	Development of documentation for IDS	1	2	3																																													
7	REC & R&D (Sheffield and/or Leicester) approval for IDS				1	2	3																																										
8	Leicester DESMOND team train educators for IDS					1	2																																										
9	Educators (Leic/SHSC) deliver test intervention							1	2	3	4	5	6	7	8	9																																	
10	Population-specific DESMOND-intervention finalised																1	2																															
11	Educators receive core DESMOND training																		1	2																													
12	Modified course available																		1	2	3	4	5																										
	RANDOMISED CONTROLLED TRIAL							**SET-UP**													**INTERNAL PILOT**														**MAIN TRIAL**											**CLOSE-OUT**			
13	Trial Management Group (or IDS group) meetings	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40	41	42	43	44	45	46	47	48
14	Develop and finalise Protocol	1	2	3																																													
15	Development of essential documentation	1	2	3																																													
16	CTRU risk assessment	1																																															
17	Coordinate collaborator contributions/feedback		1	2																																													
18	Complete IRAS	1	2	3																																													
19	Trial Steering Committee																																																
20	Initial communication with R&D			1	2																																												
21	REC submission and approval				1	2	3																																										
22	Data Management & Monitoring Plan						1																																										
23	Statistical Analysis Plan (SAP)							1	2																																								
24	Database set-up								1	2	3	4																																					
25	Randomisation System											1	2	3																																			
26	R&D Contracting and approvals							1	2	3	4	5	6	7	8	9	10	11	12																														
27	Site set-up (Files and protocol training)							1	2	3	4	5	6	7	8	9	10	11	12																														
28	Centres 1-4 screening, recruiting and randomising																	1	2	3	4	5	6	7	8	9	10	11	12																				
29	Facilitator training (centres 1-4)																																																
30	Centres 5-7 screening, recruiting and randomising																		1	2	3	4	5	6	7	8	9	10	11	12																			
31	Facilitator training (centres 5-7)																																																
32	Centres 8-10 screening, recruiting and randomising																			1	2	3	4	5	6	7	8	9	10	11	12																		
33	Facilitator training (centres 8-10)																																																
34	**NIHR ASSESS AGAINST STOP-GO CRITERIA**																																																
35	DESMOND group perform fidelity assessment																		1	2	3	4	5	6	7	8	9	10	11	12																			
36	Sheffield group perform qualitative research																		1	2	3	4	5	6	7	8	9	10	11	12																			
37	Follow-up only																															1	2	3	4	5	6	7	8	9	10	11	12						
38	Close-out, data analysis and report writing																																											1	2	3	4	5	6

Delay in IDS of approximately 2 months affects RCT tasks from month 15 accept feasibility assessment (month 25). Original timeline indicated by

The project plan is the planned schedule of activity and timing of tasks is subject to change.

1. Introduction

Background

There is an urgent need to develop interventions that lead to long term reductions in overweight and obesity in people with schizophrenia. Schizophrenia is a major psychiatric disorder that alters the patient's perception, thoughts, affect and behaviour and may involve a loss of insight. The lifetime prevalence of schizophrenia is approximately 1% (1). Mortality rates are increased 2-3 fold in people with schizophrenia and life expectancy is reduced by 10-20 years. Approximately 75% of all deaths in people with schizophrenia are caused by physical illness with cardiovascular disease being the commonest cause of death (2). Overweight and obesity contribute to this excess morbidity and mortality. Recent studies indicate that obesity is commoner among people with schizophrenia (3). Obesity occurs early in the natural history of schizophrenia with a significant proportion of people with first episode psychosis being overweight prior to any treatment. Substantial weight gain (>7%) often occurs rapidly within 6-8 weeks after treatment initiation (4).

The prevalence of obesity in the general population has increased dramatically over the last 30 years and it seems likely that the environmental changes that have provoked these increases have also affected people with schizophrenia as the rates of overweight and obesity have increased even more rapidly in people with schizophrenia (5). Individuals with schizophrenia are more likely to consume a diet that is rich in fat and refined carbohydrates while containing less fibre, fruit and vegetables than the general population (6–8).

Although no clinical studies directly link neuropathology with unhealthy food choices, these food choices may be linked directly to schizophrenia through deficient reward mechanisms (9). Thus a more widely available supply of energy dense foods may have a greater effect on those with schizophrenia. Physical inactivity and the social and urban deprivation experienced by those with schizophrenia may contribute further to the increased obesity rates (7–10).

There may be disease-specific effects of schizophrenia, such as genetic susceptibility, that have additive or synergistic actions to increase body weight further. However, the most important factor related to weight gain in people with schizophrenia is the use of antipsychotics, which are among the most obesogenic drugs. Weight gain is the commonest side effect of second generation antipsychotics, affecting between 15-72% patients (11). Other psychotropic drugs that are often prescribed to people with schizophrenia, including some antidepressants and mood stabilising drugs, such as lithium and sodium valproate, may also induce significant weight gain (12). Most weight gain occurs early in treatment (19) but longer term observational studies suggests that weight gain continues for up to 4 years albeit at a slower rate (13).

Treatment of Obesity in People with Schizophrenia

The pessimism surrounding treatment of obesity in people with schizophrenia has been challenged by a number of recent observational studies and randomised controlled trials of lifestyle and pharmacological interventions (14–16). A recently published meta-analysis of non-pharmacological interventions in people with schizophrenia (17) has shown that these led to a mean reduction in weight of 3.12 kg over a period of 8-24 weeks. In addition there were commensurate reductions in waist circumference and improvements in cardiovascular risk factors. The benefits of the programmes were seen irrespective of the duration of mental illness treatment, whether the intervention was delivered to an individual or in a group setting, whether the intervention was based on cognitive behavioural therapy or a nutritional intervention or whether it was designed to promote weight loss or prevent weight gain. Out-patient interventions appeared more effective than in-patient settings. The meta-analysis acknowledges a number of the limitations of the trials, including the small numbers of participants and the lack of long term follow-up. Most previous studies do not extend beyond 12 weeks and hence their applicability to the long term nature of schizophrenia remains unknown. The few studies reporting long term effects suggest that these may be persistent after the end of the programme for up to 1 year but others suggest that long term behaviour change is difficult to achieve (18). The meta-analysis called for longer trials with

larger numbers with a focus on weight maintenance after the initial intervention. There is also a paucity of data in people with first episode psychosis so this group are included in the STEPWISE trial.

There are several longer-term observational studies of the effects of weight management programmes. Menza et al. showed that a 52-week multimodal weight control programme led to significant improvements in weight, body mass index (BMI), glycated haemoglobin (HbA_{1c}), blood pressure, levels of exercise and nutritional knowledge in the 20 of 31 participants who completed the programme (19). A further study of 33 people with schizophrenia in Taiwan demonstrated a mean 3.7 Kg and 2.7 Kg reduction in body weight after 6 months and 1 year respectively following a 10-week multimodal weight control program (20).

A long term (8 years) observational study of a group intervention shows that further weight loss is achievable with on-going support (21). In this study of well-motivated patients, there was a progressive statistically significant reduction in mean weight and body mass index throughout the follow-up with no suggestion of a plateau. The mean weight loss was ~10% at 1 year (~10 kg), with 61% achieving a 7% weight loss. By the end of the programme, 92% (n=130) had lost some weight. The only predictor of weight loss was the number of sessions attended; gender, age, diagnosis and treatment were not related to weight loss. This suggests that an intervention of greater intensity or stronger focus may be needed in people with schizophrenia compared with the general population. Although previous studies have suggested that lifestyle interventions are hard to maintain in people with schizophrenia without support (18), there may be other factors that contributed to the achieved weight loss in this clinic. The model of care offered a multimodal programme that incorporated nutrition, exercise and some degree of behavioural interventions on the premise that weight management should not be viewed in isolation and is best combined with a holistic approach to lifestyle management. The clinic first utilised a group approach as a pragmatic low cost way forward but the group setting and peer support was also appreciated by many participants.

A group approach was also adopted by the Irish Solutions for Wellbeing programme that reported similar results (22). Lifestyle changes were not imposed on patients by health care professionals but were chosen by the participants themselves. Furthermore, many of the initial health behaviours, such as high intake of sugary carbonated beverages, were readily amenable to change. The stepwise change made the process simple, achievable and sustainable. The alternative options to lifestyle modification are limited although, a wide range of unapproved pharmacological treatments have been tried to treat or prevent antipsychotic induced weight gain (16). Most treatments have only limited effectiveness, although there is preliminary evidence from short term studies that metformin may attenuate weight gain in people taking antipsychotics (23). Metformin is also recommended for the prevention of diabetes in this patient group (24,25).

Treating obesity with either lifestyle or pharmacological interventions is both clinically and cost effective in the general population. Intentional weight loss is associated with decreased mortality and improved health (26). It is likely that similarly effective interventions for people with schizophrenia will also lead to improvements in health and would be a major step towards reducing the health inequalities experienced by people with schizophrenia. Furthermore lifestyle interventions have been shown to have modestly beneficial effects on mood symptoms that are common in people with schizophrenia. Furthermore, effective weight management strategies may lead to improved adherence to medication and reduced relapse and hospitalisation.

Structured education

Previous diabetes prevention programmes and the majority of evaluated weight loss interventions have utilised intensive one-to-one counselling strategies to promote behaviour change that are unsuitable for direct implementation within current primary care settings because of resource limitations (27). Structured education is an alternative to one-to-one counselling and refers to group-based, patient-centred educational programmes that have a clear philosophy; have a written curriculum that is underpinned by appropriate learning and health behaviour theories; are evidence

based; and are delivered by trained, quality assessed, educators (28). Structured education has been widely advocated in England as a potentially cost-effective method of promoting self-management and behaviour change in individuals with chronic disease. The National Institute for Health and Clinical Excellence (NICE) advises that structured education should be available to all individuals with type 2 diabetes from diagnosis onwards (29). Importantly, this approach has recently been adopted in the promotion of lifestyle change by the new NICE diabetes prevention guidance (25).

Intervention

This protocol describes the processes and procedures for developing the research intervention (intervention development study); and, the procedures for undertaking the randomised controlled trial of the tailored intervention. The trial will be conducted in compliance with the protocol, GCP and regulatory requirements.

DESMOND for the prevention of chronic disease

The DESMOND programme was the first nationally established structured education programme and was originally designed for people with type 2 diabetes. The original 6-hour programme was proven to be effective at promoting lifestyle change, including weight loss, and reducing symptoms of depression in a multi-centred RCT (30). In addition, a single session of the programme led to sustained improvements in some illness beliefs three years on (30). Importantly, the programme is highly cost-effective; using current real-world costs of the intervention, the lifetime incremental cost was £82 and mean incremental cost per QALY was £2,113 (31). Since 2006, the programme has been implemented in over half of all PCTs nationally (http://www.desmondproject.org.uk/); consequently within primary care, an infrastructure for delivering education programmes exists that could feasibly be utilised and extended for promoting behaviour change in people with schizophrenia.

The DESMOND intervention has been systemically tailored for use in the context of a diabetes prevention programme ("Let's Prevent Type 2 Diabetes" often abbreviated to "Let's Prevent") (32). The development of this programme was consistent with the Medical Research Council's Framework for Complex Interventions to Improve Health (33), which provides internationally recognised criteria for guiding the development and evaluation of health behaviour change programmes and international guidance on supporting behaviour change techniques for those at a high risk of developing diabetes. Let's Prevent is 6 hours long and is designed to promote increased physical activity (specifically walking), a healthy diet through reduced fat and saturated fat intake and increased fibre, and weight loss by enabling participants to self-regulate their behaviour actively using self-monitoring (feedback), relapse prevention (identifying and addressing barriers to change) and goal-setting strategies.

The programme incorporates a novel method of promoting physical activity, based on personalised pedometer use, which has been shown to be highly effective at promoting behaviour change over the longer-term, improving glucose regulation, and reducing the risk of type 2 diabetes in an overweight and obese population with impaired glucose tolerance (34,35). In addition, a standardised educator/facilitator training and quality assessment programme was developed for Let's Prevent. Using a similar approach that was developed for tailoring the DESMOND structured education programmes to the language and cultural needs of those from a South Asian background (36) Let's Prevent was specifically tailored to migrant Indian South Asians and their families (37) and is currently being tailored to adults with mild to moderate learning difficulties. This has promoted a flexible approach to patient education that accommodates the diverse needs of specific patient groups. Many of the programme's components have been recommended in the new NICE guidance on prevention of diabetes in high risk populations (25).

Patient and Professional Acceptability

Although lifestyle programmes have been introduced in some mental health settings, no research has been performed to determine the acceptability of these programmes. People with severe

mental illness have similar levels of interest in their cardiovascular health as the general population but are not always able to prioritise physical health (38). It is important to assess the acceptability of lifestyle programmes for patients and healthcare professionals. In the UK, the NICE guidance places the responsibility for physical health on primary care physicians and mental health teams. The secondary care team should maintain responsibility for monitoring service users' physical health and the effects of antipsychotic medication for at least the first 12 months or until the person's condition has stabilised, whichever is longer. Thereafter, the responsibility for this monitoring may be transferred to primary care under shared care arrangements. (39).

2. Aims and objectives

The aim of the trial will be to evaluate the extent to which a structured lifestyle education programme based on the DESMOND™ approach, when delivered to people with schizophrenia, including those with schizoaffective disorder or first episode psychosis, in a community mental health setting, can support weight loss.

Specifically, our objectives are:

1. To adapt the DESMOND™ intervention to make it more appropriate for and acceptable to mental health service users and health care professionals and to provide a greater focus on weight loss. The first phase of the research is referred to as the Intervention Development Study (IDS) throughout this protocol.
2. To undertake a multicentre randomised controlled trial in adults with schizophrenia, schizoaffective disorder or first episode psychosis to test the hypothesis that a structured self-management lifestyle education programme can lead to a significant increase in physical activity and improved diet leading to sustained clinically relevant weight loss after 1 year. The trial will include an internal pilot to assess whether it is feasible to recruit and retain people with schizophrenia in the trial.
3. To ensure fidelity of the intervention when scaled up, through a robust assessment of its delivery.
4. Through qualitative research, to assess whether the intervention when scaled up, is appropriate for and acceptable to mental health services and service users.
5. To undertake an economic evaluation of the intervention.
6. To develop a quality assurance framework for facilitators delivering the intervention.

3. Project Design

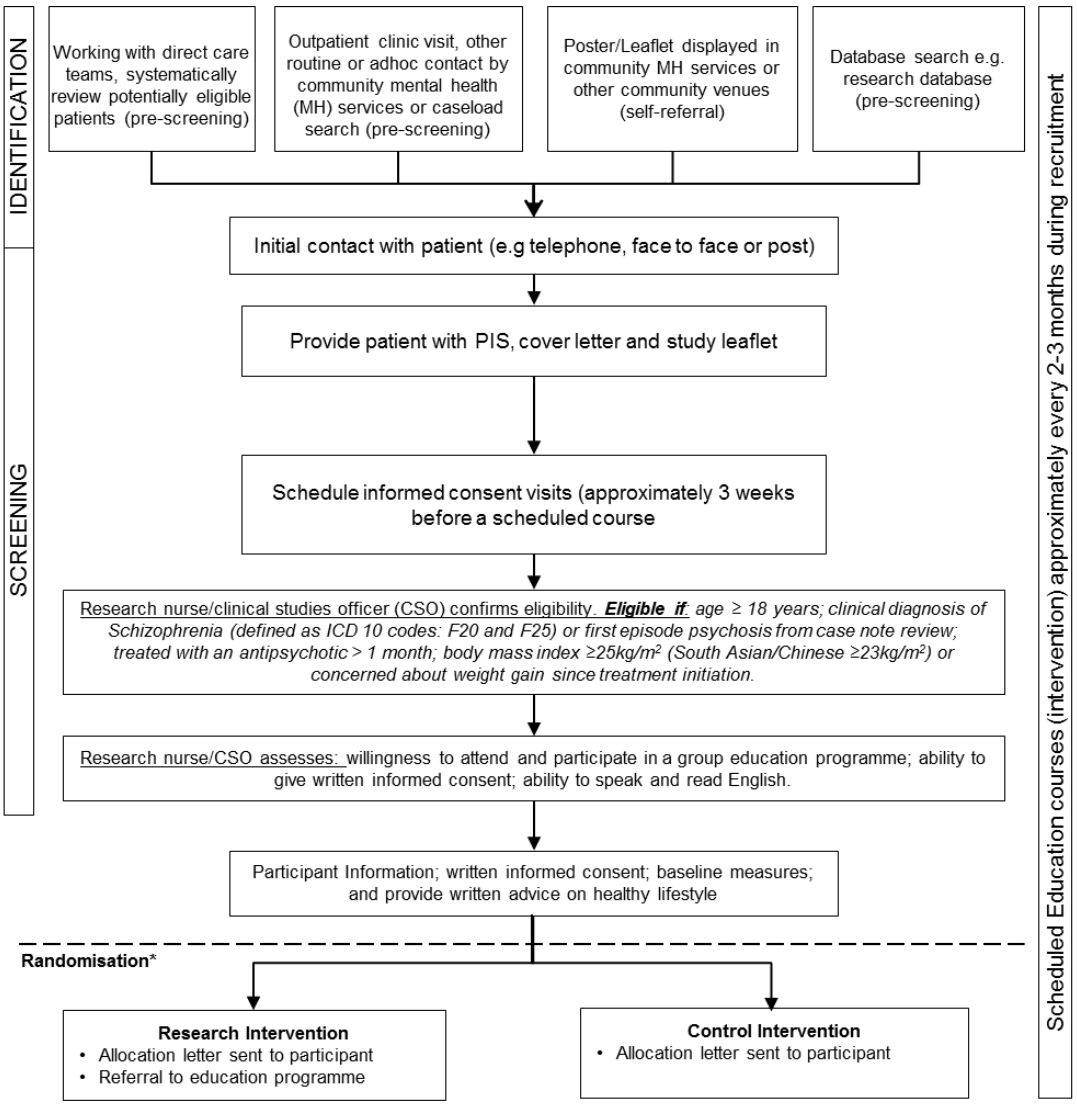
Intervention Development Study

Before the trial can commence the intervention, based on DESMOND™ Let's Prevent programme, will be developed to ensure it is fit for purpose and fully meets the needs of individuals with schizophrenia. The intervention development study (IDS) will follow an iterative process to ensure a stable intervention, which conforms to guidance from the Department of Health for "gold standard" structured education programmes and will be conducted through four stages: (1) systematic review and evidence synthesis, (2) qualitative data collection, (3) programme development, (4) programme pilot and refinement.

STEPWISE Randomised Controlled Trial

The STEPWISE trial is a multi-centre, parallel group randomised controlled trial comparing structured lifestyle education to usual NHS care to reduce or maintain weight for people with schizophrenia, schizoaffective disorder or first episode psychosis. The RCT will contain an internal pilot study between months 17 and 27. Feasibility will be assessed against stopping rules (see Section 7).

Figure 1: Trial Design



* Research activity to randomise and inform the participant of their allocation (and if allocated to the research intervention, informing the course coordinator and/or facilitator/s) should be conducted by a member of the local research team who is not undertaking outcome assessment to maintain blinding.

Design measures to minimise bias

Allocation concealment through use of a centralised web-based randomisation service;

1. Use of blinded wrist-worn accelerometry watches;
2. Participants in both arms of the study having an accelerometry watch;
3. Outcome assessors being blind to treatment allocation.

The trial will be co-ordinated from the CTRU in the School of Health and Related Research (ScHARR), University of Sheffield. Delegated study staff located at individual research sites will identify potential participants and carry out consent procedures.

Outcome assessors at each participating site will be blind to treatment allocation. Participants will be randomised using the CTRU's web-based randomisation system. A member of the site team, not blind to treatment allocation, will inform participants of their allocation. Due to the nature of the intervention participants will not be blinded. Participants will be advised that outcome assessors are blind to their allocation. If outcome assessors know (or suspect) they have been unblinded this will be recorded on the case report form and reported periodically to the trial oversight committees.

4. Selection and withdrawal of participants

Intervention Development Study

People with schizophrenia or schizoaffective disorder (defined by ICD-10 codes F20 and F25) or first episode psychosis (age ≥18 years) who are receiving care through the Community Mental Health services in Sheffield, and other sites as applicable, will be invited to participate in the Intervention Development Study (IDS). Patients will be identified during routine clinic appointments and casenote review in line with the eligibility criteria for the STEPWISE RCT and given brief information about the study. Information may be displayed in the recruiting centre/s for patients and carers; this would include contact details for the Clinical Studies Officer (or other mental health worker). If the potential participant is interested in taking part in the IDS a Clinical Studies Officer (or Mental Health worker) will contact the patient. They will read through the IDS Participant Information Sheet and answer any questions. Potential participants will be given as much time as they need to decide whether or not they want to take part in the IDS. Participants will be invited to an optional group interview (focus group). A separate consent form will be used to obtain permission to audio-record this session for those wanting to take part.

STEPWISE Trial

Selection

People with schizophrenia (defined by ICD-10 codes F20 Schizophrenia and F25 schizoaffective disorders) or first episode psychosis (age ≥18 years) who are receiving care through the Community Mental Health services in approximately 10 centres will be invited to participate in the trial. It is assumed there are between 500 and 1000 prevalent cases of schizophrenia, schizoaffective disorder or first episode psychosis under the care of each of the participating Community Mental Health services. It is estimated that ~40-70% of these individuals will fulfil the inclusion criteria, creating a pool of ~5000 potential participants. We recognise the difficulties in recruiting people with schizophrenia to clinical trials but we believe that by using 10 centres we will be able to recruit the required 396 participants (~42 patients per centre) within a 1-year time frame.

In addition, there will be ~30-60 incident cases of first episode psychosis per centre during the recruitment period. Although not all of these individuals fulfil the diagnostic criteria for schizophrenia, we intend to include people attending first episode community services in the study for the following reasons: 90-95% of people presenting with a non-affective psychotic episode (i.e. not mania and not depressive psychosis) will still meet criteria for a schizophrenia spectrum disorder 2 years later. Up to 80% of individuals treated with antipsychotics during a first episode gain more than 7% of their body weight within 3 months of treatment. People with first episode psychosis are more likely to develop weight induced metabolic abnormalities and consequently the benefits may be greater. The principles of a lifestyle intervention are likely to be no different from

those with established schizophrenia; nevertheless we will use the adaptation phase to determine whether changes are needed to take account of the relative youth and different characteristics of this group.

The 10 centres will cover a wide geographical area and include both rural and urban settings. Additional sites may be added if recruitment is lower than anticipated. The trial will be run in a variety of different community mental health locations within each centre that are convenient and /or familiar to participants including hospitals, primary care venues, residential homes and day centres identified through existing infrastructures used by the participating centres.

It is anticipated that centres will over-recruit participants to the trial. This is due to the group nature of the intervention as once a site has commenced recruitment they have to aim to recruit sufficient participants to achieve a full group in the intervention arm. Therefore, we expect to exceed the recruitment target by a maximum of 50 participants.

Systematic identification and screening

Patients will be identified during routine clinic appointments, opportunistic contact with the CMHT (including early intervention, assertive outreach and community rehabilitation services) and via searching database/s of existing patients (see figure 1). As a pragmatic trial, patients who are stepping down from inpatient to community services and who can implement the learning from the education programme (e.g. by making their own food choices and preparing meals and undertaking physical activity freely) may enter the trial. Identification of potential participants may be carried out by NHS research nurses or clinical studies officers (CSOs) acting under arrangements with the responsible care organisation taking part as a research site. Database searches may include patients who have agreed to be contacted about future research. As the intervention is delivered as a group, centres will need to identify and pre-screen potentially eligible patients systematically in preparation for the scheduled education courses (intervention). Initial contact with potentially eligible participants will be made face-to-face, by telephone or post depending on the method of identification. As far as is practicable, centres will block-book 'informed consent visits' approximately 3 weeks before scheduled education courses. This is important to ensure that participants who are randomised to receive the intervention have an opportunity to attend the education course as soon after randomisation as possible to minimise attrition and the possibility of follow-up visits occurring before the participants has received the intervention. Furthermore it will help minimise the need to cancel and reschedule courses for those allocated to the intervention group because the group size within education sessions is too small.

Centres will provide the participant information sheet and study leaflet (based on the study promotion text) via post, email or face-to-face as appropriate to potential participants in advance of the 'informed consent visit'.

Centres will monitor the number of patients booked-in for informed consent appointments and ensure, where possible, the flow of participants recruited to the study will be sufficient to ensure collection of baseline data and the viability of the scheduled intervention courses.

Eligibility

If the patient is interested in taking part in the trial a member of the site study team (research nurse or other delegate) will initiate the screening process (as described above). The process will involve assessing patient eligibility both against non-clinical and clinical criteria.

Inclusion criteria

1) Age ≥ 18 years old. There is no upper age limit.
2) Clinical diagnosis of schizophrenia or schizoaffective disorder (defined by ICD-10 codes F20 and F25) or first episode psychosis using case note review. There is no limit on the duration of illness for those with schizophrenia or schizoaffective disorder but first episode psychosis is defined as less than 3 years since presentation to the mental health team*.

3) Patients being treated with an antipsychotic. For those with established schizophrenia or schizoaffective disorder, the treatment duration should be at least 1 month prior to entry in to the trial.
4) Ability to give written informed consent.
5) Ability and willingness to attend and participate in a group education programme.
6) Ability to speak and read English.
7) Body mass index ≥25 kg/m^2 or concerned about weight. For patients from South Asian and Chinese backgrounds, the BMI threshold is reduced to ≥23 kg/m^2.

Exclusion criteria

1) Physical illnesses that could seriously reduce their life expectancy or ability to participate in the trial.
2) A co-existing physical health problem that would, in the opinion of the PI, independently impact on metabolic measures.
3) Mental illnesses that could seriously reduce their ability to participant in the trial
4) Current pregnancy, plus mothers less than 6 months post-partum.
5) Conditions associated with significant weight gain e.g. Cushing's syndrome.
6) Significant alcohol or substance misuse which, in the opinion of the PI, would limit the patient's ability to participate in the trial.
7) A diagnosis or tentative diagnosis of psychotic depression or mania.
8) A primary diagnosis of learning disability.
9) Currently (or within past three months) engaged in a systematic weight management programme.

*As the date of first antipsychotic prescription is not always available from the notes, we are using contact with the mental health services as a proxy measure of antipsychotic treatment duration. So for the purposes of the study, previous unrelated contacts with mental health services, e.g. with CAMHS, can be ignored.

The Operational Criteria Checklist for Psychotic Illness and Affective Illness (OPCRIT+) paper form will be completed from case note review to generate baseline characteristics for research purposes only. If OPCRIT+ results in a contradictory diagnosis to the clinical diagnosis, used to assess eligibility, it will not be considered as a protocol non-compliance or result in post-randomisation exclusions.

Consent procedure

During the informed consent visit a member of the research team at site will check eligibility, discuss the study with potential participants (referring to the Participant Information Sheet) in non-technical language and answer any questions. Potential participants will be given as much time as they need to decide whether or not they wish to take part. If the patient wants to take part then written informed consent will be obtained and baseline assessment carried out.

After consent and completion of baseline measures, a web-based remote randomisation system stratified by centre and time since start of antipsychotic medication up to 3 months or greater than 3 months will be used to allocate participants to either: (1) usual care; or (2) usual care plus a lifestyle education programme delivered by two trained community mental health workers. If time since start of antipsychotic medication is not known**,** an approximate duration determined by the length of time the participant has been receiving care from the CMHT is acceptable for the purpose of randomisation.

If patients who decline participation provide a reason for their non-participation, this will be recorded to help determine common reasons. This will inform the recruitment strategy as the trial progresses.

In order to follow CONSORT guidelines (40) for reporting RCTs, aggregate anonymised data on non-recruited patients will be collected. These patients will fall into three groups: eligible patients

refusing consent, eligible patients not recruited by the clinician and ineligible patients. To satisfy the requirements of the CONSORT basic data will be collected for eligible patients (those that have refused consent and those not recruited by the clinician) along with a reason for their non-recruitment (if known). To complete the CONSORT diagram, we will collect basic data and reasons for ineligibility at the participating centres.

Participants will be invited to an optional interview. A separate consent form will be used to obtain permission to audio-record the interview for those wanting to take part.

Recruitment rates and expected throughput per centre

It is well documented that the majority of public sector trials in the UK fail to recruit their original target sample within the anticipated resources (41) and that recruitment of people with schizophrenia to RCTs is more difficult than usual (42,43) for at least four reasons: (1) Substantial variations in working policy and practice between community mental health services within individual mental health trusts will often require access to team members and patients to be individually negotiated with around six teams at each centre; (2) Many people with schizophrenia under the care of the outreach teams are difficult to track and numerous home visits may be required to make initial contact; (3) Large numbers of potential participants typically decline to take part in randomised trials because of mistrust and lack of motivation; (4) Ensuring fully informed consent is more time consuming with such potentially vulnerable people than with other groups of patients. All of these factors tend to be aggravated in large multi-centre trials, which rarely confirm the leads provided by pilot studies (44).

A staggered start to recruitment is anticipated with three-four centres starting every two months between approximately Month 17 (Feb 2015) and Month 21 (Jun 2015) making a total of ten centres. Each centre will then recruit for 12 months, with contingency time available at 6 centres, before the 16-month accrual window closes at the end of May 2016. Published reports of UK-based multicentre RCTs which evaluate behaviour change interventions in people with schizophrenia are rarely CONSORT-compliant, making it difficult to assess the period over which people were recruited and therefore based on a very low recruitment rate of 0.12 participants recruited per day per trust, we anticipate being able to recruit the target sample by the end of September 2015 even if one of the ten trusts recruits nobody at all. In practice, it is likely around half the trusts will recruit much faster than other studies (e.g. Abbott (43)), but the other half may face challenges with the delivery of the lifestyle programme and retention of participants in the trial.

5. Randomisation and enrolment

The IDS does not involve randomising participants. All participants recruited will receive the test version of the DESMOND programme.

Randomised Controlled Trial

Participants recruited to the Trial will be allocated to either standard care or lifestyle intervention with a 1:1 ratio, stratified by centre and time since start of antipsychotic medication up to 3 months or greater than 3 months. An approximate duration is acceptable for the purposes of randomisation if the exact time is not known. Intervention development study

Before the trial can begin a process of developing and refining the intervention will be undertaken. The intervention development study will involve four phases in order to establish a tailored intervention for this population during the STEPWISE trial. These are described below:

1) Systematic review and evidence synthesis
The recent systematic review by Caemmerer et al (17) of the literature will be reviewed with the aim of characterising and quantifying previous self-management programmes or lifestyle intervention in adults with schizophrenia or related conditions. The review will be undertaken using systematic methodology with a predefined search strategy. The evidence will inform the education

initiative and encompass a wide range of topics including the evidence relating to psychological theories, behaviour change, education, motivation, as well as weight loss initiatives in this group of patients.

2) Qualitative component
Building on the systematic review and preliminary findings, semi-structured interviews and focus groups will be used to define the needs of adults with schizophrenia further. Semi structured interviews will be conducted with primary care and mental health providers (to inform the content, structure and delivery of the education programme), prior to curriculum development. Focus groups will be conducted with participants attending the pilot education courses and their carers, family or friends as well as the facilitators. The focus groups will be held at the end of all education sessions at a place and time that is convenient for the participants, carers, family, friends and facilitators. This will enable further refinement of the programme prior to its delivery in the RCT. All facilitators and approximately 10 participants attending the pilot courses will be invited from the Sheffield centre or other centre (if applicable) to take part in the qualitative research. Some participants will be offered the opportunity to take part in a telephone interview if they are not happy with or do not prefer the focus group. Topic guides will be used to facilitate the process of qualitative data collection, but these will be used flexibly, with scope for discussion of additional relevant topics that may arise and revision of the topic guide in line with any additional emergent issues.

All focus groups will be audio-recorded and transcribed verbatim. Data collection and analysis will be integrated and carried out by researchers at the University Hospitals of Leicester, NHS Trust. A process based on Framework methodology will be used to analyse the data collected; development of a coding frame based on key themes that have been identified; detailed coding of transcripts; charting to organise and summarise data; followed by a detailed review of the charted data to facilitate interpretation. The initial coding frame will be agreed through discussion between the qualitative researchers involved in the study, after review of a selection of transcripts; however, a constant comparative approach will be adopted whereby the coding frame will be open to revision during the detailed coding and charting stages of the process of analysis

3) Programme development
Using data generated from phase 1 and 2, the DESMOND team will work collaboratively to produce a revised version of the established structured education programme. The current 6 hour programme (32), listed in Table 1 will be adapted in line with feedback from participants in the qualitative interviews and observations made by researchers during delivery of the sessions to revise the intervention into a framework, frequency and content which will be most applicable, effective and acceptable to this patient group. It is envisaged that the programme will be condensed into around four 1.5 hour sessions in order to make it applicable to this patient group but the exact format will be dependent on findings from phase 1 and 2. Duration of sessions will be tested during the IDS. The use of 'booster' sessions and support contact (e.g. format and content) will be discussed and tested as necessary with IDS participants.
In order to support participants to make or sustain behaviour change the following will also be developed to use in the RCT:

a. 3 booster sessions post education at 4, 7 and 10 months (post-randomisation)
b. Support contact from a community mental healthcare professional every two weeks. This will either be a 10 minute face to face appointment or 10 minute telephone call, text messaging or motivational postcards.

Table 1: DESMOND Let's Prevent Curriculum

Session 1	**Theory**	**Sample Activity**	**Duration**
Introduction	-	-	10 mins
Patient story	CSM	Participants asked to tell their story about how they discovered they had pre diabetes and their current knowledge of pre diabetes	30 mins
Professional story	CSM DPT	Uses participants' stories to support them in learning how the body regulates glucose	50 mins
Taking control 1 Weight management	CSM, DPT, SLT	Uses participants' stories to support them in discovering how weight/waist affects pre diabetes. Provides knowledge and skills for food choices to control weight	30 mins
Physical activity	CSM, DPT, SLT	Uses participants' stories to support them in discovering how physical activity affects pre diabetes. Provides knowledge and skills for activity choices to manage pre diabetes	40 mins
How am I doing?	SLT	Participants reflect on what issues have come up in the programmes so far	5 mins
Session 2	**Theory**	**Sample Activity**	**Duration**
Reflections	SLT	Participants reflect on issues that have arisen in the programmes so far	10 mins
Professional story	CSM	Uses participants' stories to support them in discovering how other risk factors (e.g. blood pressure and cholesterol) affect pre diabetes and development of complications	30 mins
Taking control 2 Food choices: focus on fats	DPT, SLT	Provides knowledge and skills for food choices to reduce risk factors	50 mins
Self management plan	SLT	Participants supported in developing their self management plans	30 mins
Questions	CSM	Checks that all questions raised by participants throughout the programme have been answered and understood	40 mins
What happens next?	SLT	Follow up care outlines	5 mins

CSM: Common sense model, DPT: Dual processing theory, SLT: Social learning theory.

In order to assess the effectiveness of these interventions participants, carers, family or friends, facilitators and service providers will be asked about them during the focus groups and/or telephone interviews.

There will also be provision of resources to encourage attendance at education sessions: water bottles, pedometers, healthy perishable foods (options drink sachets, dried fruits etc.)

4) Programme refinement (IDS with patients)
An iterative development cycle based on an established method developed by the DESMOND collaborative for refining and tailoring structured education programmes to specific groups will be used. This method involves features of action research that incorporates both qualitative and quantitative research methods to refine the content of the curriculum, resources and develop the educator/facilitator training programme. Initially, the programme will be delivered to a representative group of approximately 7-10 individuals who may or may not choose to be accompanied. The feedback of accompanying people will also be incorporated into the iterative cycle. Quantitative data (short term assessment of psychological and behavioural factors) and qualitative feedback from participants and educators will then refine the programme. The refined programme will be re-piloted to a new group of approximately 7-10 patients and those accompanying them, who will also provide feedback as described earlier. Based on previous research by our group, this cyclical process needs to be conducted at least twice. Around 15 individuals plus accompanying people in total are likely to be involved. This work will be conducted within the Sheffield Centre. If further iterations of the programme are required, these may be conducted at the Sheffield centre or other centres involved in the project. Participants who agreed to take part in the IDS will be invited to attend one or more refresher sessions. This will enable piloting of booster session content to be delivered during the RCT. IDS booster sessions will last approximately 2.5 hours (including breaks) to reflect the increased duration of group sessions as a result of piloting the foundation course.

STEPWISE Trial

Research Intervention

We will deliver a structured lifestyle education programme that encourages increased physical activity, improved diet and weight reduction in people with schizophrenia, schizoaffective disorder or first episode psychosis. The programme will be based on the DESMOND™ approach, which provides person-centred structured group self-management education for people with, or at risk of, type 2 diabetes, and which uses a described philosophy and psychological theories of adult learning.

The DESMOND™ philosophy recognises that individualising health risks may improve motivation. While it is important not to minimise negative messages, such as, the complications of obesity, these will be followed by positive messages of behaviour change. The DESMOND™ approach provides an opportunity for individuals to develop a personal action plan to take control of their own situation. As in all DESMOND™ modules, individuals will be supported to identify their own health risks and then respond by setting personalised goals which are behavioural and specific. Supporting people to be confident self-managers of their weight is essential to achieving these goals.

The adapted programme developed during the IDS, which will form this intervention, is likely to include the following sessions: the participants' story about their weight, understanding weight and the links to medication, food and activity, taking control of weight and goal setting. The programme will be supported by specially developed resources which may include: a patient food and activity diary, goal setting worksheets & other materials. The intervention will be delivered in a community setting using trained facilitators (educators). Administration of the intervention, including booking venues and reminding participants about their course (e.g. by phone or other appointment notification) will be provided by centres to support facilitators running the course. Although the content and structure of the programme will be based on the Let's Prevent programme, it will be tailored to the patient group during the Intervention Development Study.

The adapted intervention will be available as a written curriculum to ensure consistency, no matter where it is delivered. Resources will include patient support material especially written or produced for the adapted intervention and in line with meeting its patient centred philosophy. Participants will not be 'taught' in a formal way, but rather supported to discover and work out knowledge, and to allow this to inform the goals and plans they make for themselves.

As the aim of our current intervention is to achieve weight reduction, this target will have greater prominence; however, it is recognised that the other targets will help the participant achieve weight loss. Furthermore, weight reduction should not be regarded solely as a final outcome but also as a means of reducing weight related morbidity, including type 2 diabetes.

The programme will consist of a foundation programme followed by "booster" sessions delivered at approximately 4, 7 and 10 months (post-randomisation). The foundation programme will be delivered by two trained community mental health workers to groups of approximately 6-8 individuals in four sessions. There may be a fewer or greater number of participants in each group depending on the rate of accrual and the level of dropout. Each session will last approximately 2.5 hours (including breaks) and usually take place once per week. See Figure 2 and Figure 3 for an outline of the adapted programme developed during the IDS.

Figure 2: STEPWISE Foundation Sessions Curriculum Outline

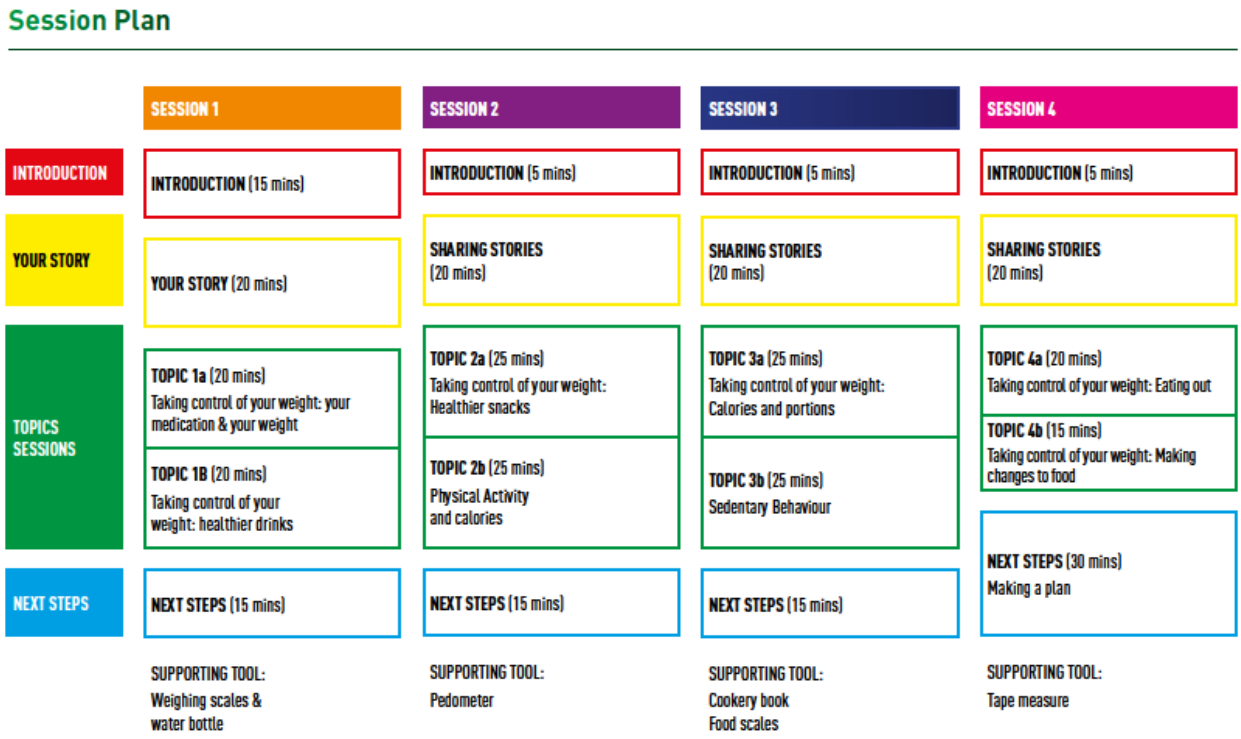
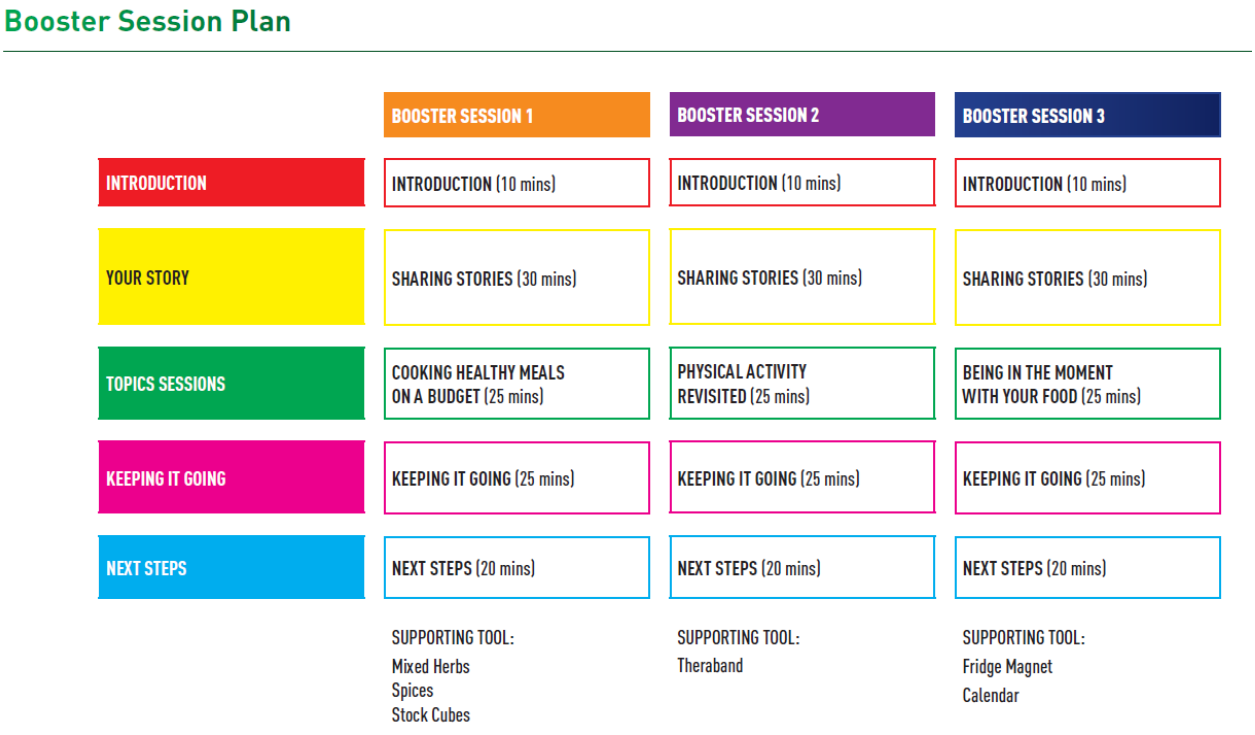


Figure 3: STEPWISE Booster Sessions Curriculum Outline



Pre-course information
Participants allocated to the research intervention will be contacted by the session coordinator (administrator) and provided with pre-course information (e.g. introductory letter and leaflet) which will confirm when the sessions will take place and what to expect.

Support contact
In order to support behaviour change, community mental health workers (trained facilitators) will remain in contact with the participants, in the intervention arm, approximately every 2 weeks, approximately 10 minutes each time. Ideally, this contact will be personalised and be carried out face to face or by telephone, the preferred method of contact can be identified by the participants; where face-to-face telephone support contact is not possible, a personalised letter/postcard will be sent to participants. The use of text messaging or other social media as a means to support the participants will be informed by the qualitative interviews as part of the Intervention Development Study. The facilitator providing the support will be provided with training, developed by the Intervention Development team during the IDS phase.

In order to assess treatment fidelity of these support contacts a quality development tool will be developed to find out e.g. how participants were contacted; face to face or telephone call (this will help us to see which worked better and had good outcomes), how long the contact was for etc.

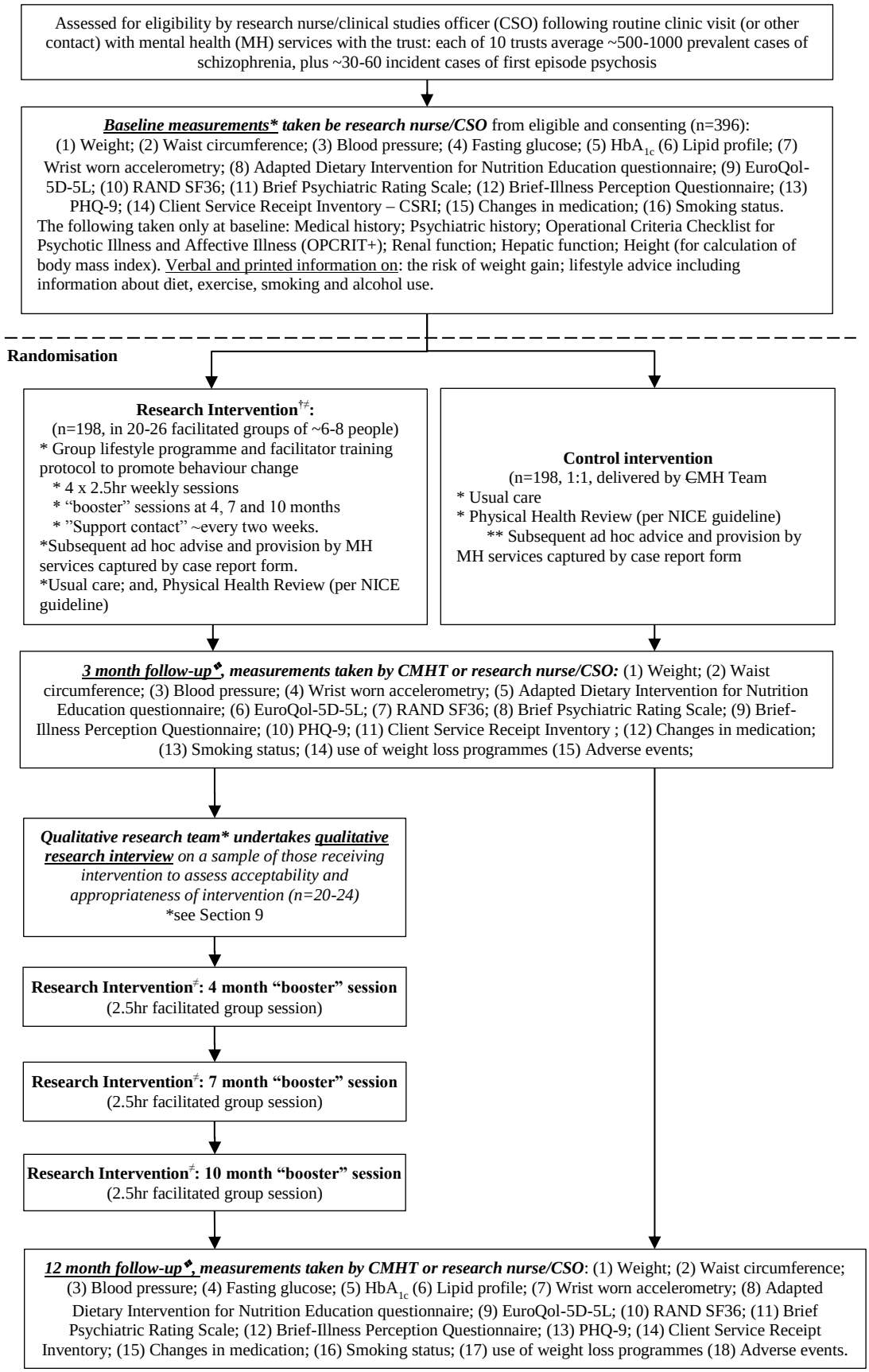
Control Intervention

People with schizophrenia are generally followed up by multidisciplinary community mental health teams as well as primary health care services in community settings using the care programme approach. Treatments offered within the teams include antipsychotic medication, cognitive behavioural therapy, family interventions and support to aid social inclusion & vocational activity. Over recent years more attention has been paid to physical healthcare of people with schizophrenia. The NICE guideline on the treatment and management of schizophrenia recommend an annual physical health review. These include recording of blood pressure, weight/BMI, glucose and lipid profile and appropriate management as needed.

Despite this guidance, significant variability exists in the provision of physical health care, with interventions often only offered when problems such as obesity and diabetes develop. When antipsychotics are prescribed, people with schizophrenia are often informed of the risk of weight gain and may be given ad hoc lifestyle advice. This usually includes information about diet, exercise, smoking and alcohol use but again practice varies.

Although weight gain is recognised by clinicians to be a common problem for people with schizophrenia, intervention is often delayed. The response to reported or observed weight gain is often to give further lifestyle advice. People may have access to local referral for exercise schemes and weight management groups. As weight gain is frequently attributed to medication by the person with schizophrenia and clinical staff, the antipsychotic is often switched to another drug. Although some people lose some weight after changing drug, many do not and there are risks of relapse from differing efficacy of the alternative drug. Furthermore, the new drug may also be associated with problematic side effects.
Centres will provide usual care to participants in the control arm taking account of NICE guidelines. In order to standardise usual care in the control group (and intervention group), as far as possible, centres will undertake a physical health review as per the NICE guideline. Centres will provide printed advice to participants on the risk of weight gain and lifestyle advice, including information about diet, exercise, (e.g. Change4Life “Swap it Don’t stop it”); and, smoking and alcohol use (as appropriate). All participants will receive the printed advice at baseline (prior to randomisation). We will (1) record any uptake of weight management and/or physical activity programmes by participants during the study and (2) collate information from centres about uptake of NICE recommendations more widely.

6. Assessments and procedures



†Number of sessions included in adapted DESMOND intervention subject to change, based on findings of Intervention Development Study
* Baseline wrist watch and fasting blood sample may be collected after randomisation (but before intervention delivery). ≠ STEPWISE Session Feedback form. ❖ A follow-up visit window of -2/+4 weeks will be set to allow time for missed or rescheduled appointments. At 12 months, collection of the fasting blood test can be up to 5 weeks after the 12 month visit takes place and combined with collection of the watch.

Outcome measures

The following measurements will be taken only at baseline: medical history; psychiatric history, Operational Criteria Checklist for Psychotic Illness and Affective Illness (OPCRIT+); renal function; hepatic function; height (for calculation of body mass index).

Primary Outcome measure

The primary objective of this trial is to evaluate the effectiveness of structured lifestyle education on reduction of weight gain for people with schizophrenia, schizoaffective disorder and first episode psychosis.

Primary endpoint: Change in weight (kg) at 12 months after randomisation.

Secondary Outcome measures

Secondary outcomes include biomedical, behaviour change and psychosocial factors including quality of life, health beliefs and cost-effectiveness. All secondary outcome measures will be assessed at baseline and after 3 and 12 months (except where stated) to measure if there is an effect and if so, whether this is sustained over the longer term.

Secondary endpoints:

1) Weight; the proportion who maintained or reduced weight; percentage change in weight;
2) Waist circumference;
3) Body mass index;
4) Wrist worn accelerometry (up to 7-day GENEActiv);
5) Adapted Dietary Changes (Dietary Instrument for Nutrition Education questionnaire (45));
6) Blood pressure, measured by electronic sphygmomanometer in the non-dominant arm after 5 minutes rest;
7) Fasting glucose, lipid profile and glycated haemoglobin (HbA_{1c}) (baseline and one year only);
8) EQ-5D 5L (46);
9) RAND SF36 (47);
10) Adapted Brief Illness Perception Questionnaire (B-IPQ) (48);
11) Brief Psychiatric Rating Scale (49);
12) Changes in medication including doses and side effects;
13) Smoking status;
14) Service use and costs (Client Service Receipt Inventory) (50);
15) Patient Health Questionnaire 9 (PHQ-9) (51);
16) Use of weight loss programmes (follow-up only);
17) Adverse events (follow-up only);
18) Session Feedback (intervention only).

Fasting blood test

A fasting blood test should be collected at baseline and 12 month follow-up. A visit window of up to 4 weeks between the baseline visit and blood test has been set because a fasting sample may not be possible at the baseline visit (if combined with the 'informed consent visit'). The sample (as with all baseline data) should be taken before start of intervention delivery; however, the blood sample collection may occur after randomisation (which is more likely when participants are recruited close to the start of scheduled intervention courses). This will also allow centres to take the blood sample at the same time as collecting the accelerometer. Therefore up to 5 weeks will be permitted between the 12 month follow-up visit and collection of a fasting blood sample. At baseline, collection of the accelerometer may also occur after randomisation. If a participant has had a fasting blood test within the 4 weeks prior to either baseline or 12 month follow-up, and does not want a repeat test, the result can be recorded on the CRF instead of taking a fresh sample.

OPCRIT

A window of up to 10 weeks post-baseline assessment is permitted to complete the OPCRIT from case note review. Completion of OPCRIT is based on a lifetime ever occurrence from patient notes therefore the window will allow more time to collect data especially where paper records are not readily available (e.g. archived). The minimum dataset is checklist item numbers 1 – 90. Where there is insufficient data to result in an OPCRIT diagnosis this will be recorded in the trial database.

Follow-up

The follow-up visits will be performed at 3 and 12 months from the date of randomisation. A visit window of -2 weeks to + 4 weeks has been set to allow for missed or rescheduled appointments. The fasting blood test at 12 months can be conducted up to 5 weeks after the follow-up due date to allow collection of a fasting sample at the same time as centres retrieve the accelerometer.

A summary of data collection and time points is outlined in Figure 4.

Figure 4: Summary of instruments and assessments

	Before baseline	Baseline	Randomisation	3 month follow-up	12 month follow-up
Eligibility criteria assessed by clinical care team	●				
Medical history		●			
Psychiatric history		●			
Operational Criteria Checklist for Psychotic Illness and Affective Illness*		●			
Renal function**		●			
Hepatic function**		●			
Height (to calculate body mass index)		●			
Weight		●		●	●
Waist circumference		●		●	●
Wrist worn accelerometry (GENEActiv) up to 7 days**		●		●	●
Adapted Dietary Instrument for Nutrition Education (DINE) questionnaire		●		●	●
Blood Pressure (BP)		●		●	●
Fasting glucose**		●			●
Lipid profile**		●			●
Glycated haemoglobin (HbA_{1c})**		●			●
EQ-5D-5L		●		●	●
RAND SF36		●		●	●
Brief Illness Perception Questionnaire (B-IPQ)		●		●	●
Brief Psychiatric Rating Scale		●		●	●
Smoking status		●		●	●
Client Service Receipt Inventory (CSRI)		●		●	●
Changes in medication (dose and side effects)		●		●	●
Patient Health Questionnaire 9 (PHQ-9)		●		●	●
Use of weight loss programmes				●	●
Adverse events				●	●
Randomisation			●		

*The paper form will be completed by centres from case note review. Paper forms will be returned to CTRU for data entry. ** May be collected after randomisation.

The data will be used to calculate the 10 year cardiovascular disease risk and Leicester diabetes risk scores.

Intervention attendance
Attendance (or not) at group and one-to-one intervention sessions will be recorded on the CRF. Non-attendance at session/s will not be recorded as Protocol non-compliance. Course materials from a missed session may be provided by facilitators, where this will assist participants learning or implementation of the education programme.

Participants attending education sessions will be invited by facilitators to complete the 'Session Feedback' form at the end of each session. Participants are not encouraged to bring someone with them to the intervention sessions; however, if they do this will be recorded on the case report form and not considered Protocol non-compliance.

Intervention withdrawal

If a participant decides to withdraw from the education programme, this will be recorded on a case report form including the reason for withdrawal (if known). The participant will be followed-up unless the patient explicitly also withdraws consent for follow-up (data up to this time will be included in the trial). The reason for withdrawal of consent to the trial will also be recorded if known.

Lost to follow-up

Participants will be considered 'lost to follow-up' if they do not complete 12 months outcome data.

Study completion

The end of the trial is defined as the date of the last follow-up (including qualitative sub-study where applicable) of the last patient in the trial.

Safety Assessments

There are few anticipated adverse effects of the structured lifestyle intervention. The Intervention Development Study will ensure that it is tailored to the needs of people with schizophrenia (including patients with schizoaffective disorder or first episode psychosis). There is a risk that anxiety about weight and its complications may be increased. If the intervention is unsuccessful this may lead to feelings of poor self-esteem. These risks are outweighed by the risk of widening health inequality and worsening health among people with schizophrenia if the intervention is not assessed.

Serious Adverse Event (SAE)
Definition
An SAEs is an event that:
(a) results in death;
(b) is life-threatening* (subject at immediate risk of death);
(c) requires hospitalisation or prolongation of existing hospitalisation**;
(d) results in persistent or significant disability or incapacity;
(e) consists of a congenital anomaly or birth defect
(f) is otherwise considered medically significant by the investigator***.

* 'life-threatening' in the definition of 'serious' refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.
**Hospitalisation is defined as an inpatient admission, regardless of length of stay, even if the hospitalisation is a precautionary measure for continued observation. Hospitalisations for a pre-existing condition, including elective procedures that have not worsened, do not constitute an SAE.

***Other important medical events that may not result in death, be life-threatening, or require hospitalisation may be considered a serious adverse event/experience when, based upon appropriate medical judgment, they may jeopardise the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

Any serious adverse events which a member of the study team (e.g. research nurse, research assistant) deems to be associated with the trial intervention should be assessed by the local Principal Investigator.

Expected adverse events
There are serious adverse events that are expected for the patient population:
(a) psychiatric hospitalisation;
(b) self-harm;
(c) suicide attempt;
(d) death from suicide.

Suspected Unexpected Serious Adverse Events
SAEs that are both "unexpected" (that is, the type of event is not listed in the protocol as an expected occurrence); and "related" (that is, it resulted from administration of any of the research procedures). Any serious adverse event that meet the criteria above will be reported on an adverse event form on the case report form and database. will be reported by the site in accordance with CTRU SOP PM004 to both the Clinical Trials Research Unit and to the Sponsor **within 24 hours of the discovery at site**. Expedited reporting will be conducted by the sponsor (or their delegate) to the Research Ethics Committee within the timeframes specified by the Health Research Authority for non-CTIMP studies.

A member of the site study team will enquire about any adverse events since the previous visit and record these on the adverse event paper CRF and database. For any SAEs, a SAE paper CRF and database entry will be completed **within 1 week of completing the paper form**. The event will be assessed by the local Principal Investigator and the form will be kept in the Site File. Serious Adverse Events will be reported in the periodic safety reports to the Research Ethics Committee, Trial Steering committee and Data Monitoring and Ethics Committee.

Risk

The participants clinical care team is responsible for all patient level treatment and management decisions – including assessment of risk. Risk should be documented in the patient's record by their care team. This should be in line with the Trust risk management and safeguarding policy and Good Clinical Practice. Whilst in the trial should a participant's mental state deteriorate or risk (whatever type; including, expressed thoughts of self-harm or harm to others) is encountered, the researcher will follow local risk management policies. Any concerns will be referred to the clinical care team (e.g. Care Coordinator, Key Worker or Consultant) and the referral including reason for cause will be documented.

If a participant is discharged from the mental health trust's care during their participation in the trial, they will remain the responsibility of the Principal Investigator. Blood test results will be shared with the participant's GP to ensure ongoing clinical monitoring.

7. Statistics

Intervention Development Study

No statistical considerations apply to the intervention development study.

STEPWISE Trial

Sample size
The primary outcome is change in weight (kg) at 12 months after randomisation. The sample size calculation is based on data obtained from two sources, both of which evaluated behavioural interventions for weight loss in patients prescribed antipsychotics for schizophrenia. Das et al (2012) undertook a systematic review of randomised and non-randomised controlled trials which reported between-group differences of 1.5kg-6kg with standard deviations typically around 5kg (52). The second source was data on overweight and obese UK patients with severe mental illness in which 51 patients with schizophrenia were followed up for at least one year; among these, the weight change was 7.7kg with a standard deviation of 6.5 kg (21). We propose to detect a difference of 4.5kg, which is both clinically meaningful (being on average around a 5% reduction in body weight) (53) and appears compatible based on previous work. Assuming a conservative estimate of the standard deviation (SD) of 10 Kg, 95% study power, and two-sided significance level of 5%, 130 participants per arm (260 in total) are required in order to detect a minimum clinically important difference of 4.5 Kg.

Since the intervention is delivered in groups rather than individually, the outcomes of the participants within the same group may be correlated (we assume negligible correlation among patients in the control arm). Assuming on average 7 participants per group, and an intra–class correlation of 5% in the intervention arm, the sample size will be inflated by a design effect of 1.3 in the intervention arm in order to allow for this, which yields revised sample sizes of 169 and 130 in the intervention and control arms respectively (299 in total). To maintain a 1:1 allocation, 158 patients per arm are required to reproduce this power. We further anticipate a conservative dropout rate of around 20% (higher than that observed in similar studies (54)), giving a final total of 198 participants per arm. With 10 centres, this requires 40-50 participants per centre (rounded upwards), 20-25 of whom will receive the intervention in 3 or 4 groups.

At the end of the internal pilot, an assessment will against the following criteria:

Stopping Rules
By 11 September 2015, the middle of project (month 24):
1. Ten centres should have been initiated and should have recruited their first participant
2. 250 participants should have been recruited
3. Six centres should have completed their first STEPWISE course
4. 96 participants should have been followed up to their three month outcome assessment

The trial will be considered infeasible and will be stopped if, on 11 September 2015, one or more of the following conditions apply:
1. Fewer than six centres have recruited their first participant.
2. Fewer than 125 participants have been consented.
3. Fewer than three centres have completed their first four-week STEPWISE course
4. Fewer than 75% of those followed up to their three month outcome assessment have contributed valid weight (primary outcome at 12m) data at this time point.

Statistical analysis
Since this is a parallel group, randomised controlled trial, with a usual care (control) arm, data will be reported and presented according to the revised CONSORT statement (40,55). The analysis will be performed on an intention to treat basis and all statistical tests will be two-tailed at 5% significance level. Demographics and characteristics of participants at baseline will be summarised and assessed for comparability between the intervention and control arms (56,57).

The primary objective of the main phase of the trial (weight at 1 year post randomisation) will be assessed by fitting a marginal generalised estimating equation model (GEE) adjusted for baseline weight, using robust standard errors and an exchangeable correlation structure. This model incorporates an adjustment for potential clustering or correlation among the outcomes of participants treated in the same group. A 95% confidence interval for the difference in weight between the lifestyle intervention and control arms will be reported with its associated P-value. A sensitivity analysis will be performed in the same manner alongside this unadjusted analysis which will include baseline covariates and any observed imbalances. In case of missing data, the missing data mechanism will be explored and multiple imputation approach applied to assess the robustness of the findings.

Of key interest is whether the intervention conveys the same effect among recently diagnosed patients (i.e. patients experiencing first episode psychosis) as it does among those established on anti-psychotic medication for a greater period of time. We will investigate this in the analysis by fitting an interaction term between treatment group and the time since starting anti-psychotic medicine (including a non-linear term if appropriate). The treatment effect will be presented graphically for different subgroups of the time elapsed since commencing medication.

Other continuous outcomes will be analysed and reported in the same manner as the primary outcome. Analysis of binary outcomes will be undertaken using a marginal generalised logistic linear regression model within the GEE framework and difference between treatment groups will be reported as odds ratios with associated 95% confidence intervals and P- values. Further details will be provided in a separate statistical analysis plan in accordance with CTRU SOP ST001.

Economic evaluation
The economic evaluation will be conducted from a health and social care and societal perspective. The number of intervention sessions received will be centrally recorded. The cost of the intervention will be based on staff time plus overheads (capital and administrative) and an element for training and supervision. Other service use will be recorded at baseline, and at 3- and 12-month follow-up using the interviewer-administered Client Service Receipt Inventory (50), and will include:

- primary care;
- secondary care (specialist mental health and physical health services);
- social care;
- psychotropic and other medication; and,
- informal care from families or friends (expressed in terms of hours per week spent on specific tasks because of the participant's health problems).

Service costs will be calculated by combining the above data with appropriate unit cost information (i.e. Curtis, 2012; NHS Reference Costs, British National Formulary). Informal care time will be valued using average wage rates with sensitivity analyses using minimum wage rates and the value of a homecare worker. Lost work time will also be recorded for those in employment and valued using average wage rates. Total health and social care costs and societal (i.e. including informal care and lost employment) costs will be reported and compared between the two groups for the 1-year follow-up. A regression model will be used with baseline costs controlled for and bootstrapped 95% confidence intervals generated given

the expected skewed cost distribution. Cost –effectiveness will be assessed by combining the cost data (from both perspectives) with the primary outcome measure and QALYs. The latter will be generated from the EQ5D using UK tariffs and area under the curve methods. If the intervention results in lower (higher) costs and better (worse) outcomes then it will be dominant (dominated). In the event of higher costs and better outcomes (or lower costs and worse outcomes), incremental cost-effectiveness ratios (ICERs) will be constructed to show the cost per extra unit of weight loss or extra QALY gained. Uncertainty around the ICERs will be addressed by constructing cost –effectiveness planes using 1000 bootstrapped cost-outcome pairs and cost-effectiveness acceptability curves (CEACs). The latter will indicate the probability that the intervention is more cost -effective than treatment as usual for different threshold values placed on a unit reduction in weight or one more QALY gained. NICE uses a threshold of £20-30K for a QALY gain and so the CEACs will include this value in the range of values. There are no recognised threshold values of a unit reduction in weight and so values will be reported at which the intervention or treatment as usual has a 50%, 70%, 80% and 90% likelihood of being the most cost -effective option.

Sensitivity analyses will be conducted by varying the costs of the intervention, informal care and lost employment. QALYs based on the SF6D will also be used in sensitivity analyses given that this arguably has better distributional properties than EQ5D-based QALYs in this patient population (58). The EQ5D has a clear ceiling effect in people with schizophrenia while the SF6D (derived from the RAND SF36) is normally distributed.

8. Trial Ancillary sub-studies

Introduction to the Trial sub-studies

A process evaluation will be undertaken "to explain discrepancies between expected and observed outcomes, to understand how context influences outcomes, and to provide insights to aid implementation" (33). As the MRC framework is vague on what a process evaluation should contain (59), we will use a modified version of Linnan and Steckler's framework for process evaluation (60). We will explore the context for intervention implementation using qualitative methods. We will explore reach and recruitment quantitatively through information collected for the CONSORT diagram, bearing in mind that the requirement for randomisation affects the external validity of estimates of reach. The methods of recruitment will also be explored qualitatively. The dose delivered and received - assessed quantitatively through facilitator registers. Fidelity will be measured by the DESMOND team. We will not produce a composite score for implementation as proposed by Linnan and Steckler, as we do not believe such a score would have face validity or utility for our intended audience.

Qualitative component of STEPWISE trial

The qualitative research component will investigate whether the intervention, when scaled up, is appropriate for and acceptable to mental health services and service users. The qualitative research will also inform the quantitative aspects of the process evaluation.

Service Users

The semi-structured interview topic guide will contain general open questions exploring the experience and acceptability of the intervention to participants. The guide will also include questions intended to elicit themes outlined in the existing published literature such as the barriers to, and facilitators of, the use of lifestyle interventions in people with schizophrenia (61–63).

Participants in the research intervention arm will also be invited to complete a feedback form at the end of each session (STEPWISE Session Feedback). The forms will be returned to CTRU for data entry and will not be read by facilitators.

Facilitators delivering the intervention
The process evaluation will explore health professional views on the experience of incorporating the lifestyle intervention into practice through individual semi-structured interviews. Topic guides will explore how this complex intervention is normalised within mental health trust practice. Topic guides may be piloted during the IDS.

The themes that emerge from the literature centre around the interventionists perceived validity of the intervention and its transferability to routine practice. May's 'normalization process theory' (NPT) will be used as a theoretical framework to better understand the conditions necessary to support the introduction, embedding and integration of protocolised lifestyle interventions as routine elements of care (64). While NPT emphasises the influence of social systems on behaviour, the study will also utilise relevant domains from the Theoretical Domains Framework (TDF) (65,66) which emphasises individual influences on behaviour. We will also collect facilitator characteristics (e.g. level of education).

The process evaluation will inform the interpretation of the trial results and subsequent policy-making, in line with the MRC's Complex Intervention Framework (33).

Method
The patient sample for the qualitative sub-study will involve approximately 20-24 patients receiving the lifestyle intervention, purposively sampled to recruit different genders and ages. Interviews will be held after the end of the intervention and three month follow-up, be conducted face-to-face (venue of participant's choice) or via telephone (audio or video call depending on participant's choice) by a member of the research team (Hind, Rebecca Gossage-Worrall, study manager, or CTRU Research Assistant) and will last about 1 hour. Due to the location of the ten centres most interviews will be conducted via telephone.

Interviews with interventionists (facilitators) will be conducted via telephone (audio or video call depending on facilitator's choice) or face-to-face (by DH, RG-W or CTRU Research Assistant) and continue in each group until data saturation is complete. We expect this may mean approximately 20 interviews with a purposive sample of 20 interventionists will be completed.

All semi-structured interviews will be audio-taped and fully transcribed. Data will be managed using Nvivo (QSR Interventional). Using the National Centre for Social Research 'Framework' approach (67), transcripts and notes will be read and re-read independently by two members of the research team (Hind and, Gossage-Worrall, Kath Barnard, health psychologist, or patient representative, Angela Etherington for the patient interviews); Hind and Barnard for the clinician interviews). Themes of *a priori* interest will be identified through review of the literature during the intervention development study and through consultation with our service-user representatives; theoretical perspectives from NPT and TDF will be drawn on to inform themes and interpretation of data. Subthemes within umbrella categories will be derived inductively from reading the transcripts. DH, RG-W, KB and AE will undertake all stages of the analysis of patient transcripts: familiarisation; identifying a thematic framework; indexing; charting; and, mapping and interpretation. We will actively seek 'deviant' or 'negative' cases and modify emerging themes accordingly (68). Training for AE will be provided by DH.

Facilitator training and assessment of intervention fidelity
A fidelity assessment will be undertaken to investigate whether the intervention can be delivered faithfully when scaled up. As for the facilitators' delivery of the intervention is key, an assessment of facilitator performance in each of the participating centres will be conducted during the RCT.

The facilitator training programme and intervention fidelity checks will be undertaken through the DESMOND collaborative, and based on the standardised and established criteria currently used to provide quality assurance in the DESMOND National Programme. Infrastructure

developed through the DESMOND collaborative will be used to train groups of at least 4 facilitators per research site. Facilitator recruitment will take place from local NHS centres and other suitable settings. Facilitator training will consist of a 3 day training programme for health care professionals with expertise in mental health, and will be preceded by a set of preparation exercises. Training is interactive, and follows the philosophy and psychological principles that underpin patient education initiatives. Modelling is therefore an important feature of training. Facilitators will be encouraged to develop as reflective practitioners throughout the training and mentorship process, through use of tools well established in the DESMOND™ national programme which will be adapted to fit the requirements of the STEPWISE programme. These tools support the development of essential competencies in novice facilitators. An additional training day will be provided to ensure facilitators can deliver booster sessions.

In order to ensure that the programme philosophy and content are being adhered to, intervention fidelity, that is, in terms of facilitator performance, will be checked in each centre, based on the approach used for the DESMOND™ programme (69), which won a Health Service Journal award for its high quality and relevance to the NHS.

During the trial, the delivery of individual facilitators at each centre will be assessed against criteria derived directly from the STEPWISE programme. This will enable the study team to identify there is any deviation from the delivery taught in training, and will also provide evidence for establishing a benchmark for delivery and facilitator Competencies when the intervention is scaled up. All training and assessment procedures will be supportive and transparent.

Although it is not possible to identify the final suite of intervention fidelity tools, these are likely to include assessment of content delivery; assessment of facilitator behaviour against a set of criteria derived from the STEPWISE programme itself; assessment of facilitator talk time, using the DESMOND Observational Tool (DOT). The latter assessment involves an independent assessor scoring activity in the session (e.g. who is speaking; miscellaneous activity) through use of a 10 second audio prompt (audible only to the assessor). It has been shown that the amount of time facilitators or participants spend speaking, is predictive of the changes observed in the participants' illness perceptions: less facilitator talk leads to a greater change in participants' beliefs about their condition (53), and is a precursor to behaviour change. Intervention fidelity assessments will be used to inform outcomes of the trial.

9. Further research

Participants will be offered the option to consent to be contacted about further research at their 12 month follow-up visit. If the participant is interested, they will be asked to sign a short consent form.

Participants who have completed 12 month follow-up and whose involvement in the study has already completed will be invited, via their clinical care team, to consent to be contacted about further research. If the NHS Trust operates a research database (where consent to contact about research is already in place) or an opt-out system, researchers acting under arrangements with the responsible care organisation will contact the patient directly about the option to be contacted about further research relating to STEPWISE.

10. Trial supervision

The STEPWISE RCT will be registered with the local R&D department of each research site. Three committees will be established to govern the conduct of this study:

- Trial Steering Committee (TSC);
- Data Monitoring and Ethics Committee (DMEC);
- Trial Management Group (TMG).

These committees will function in accordance with Sheffield CTRU SOPs and voting members of the TSC and DMEC will be approved by the grant awarding body. As a minimum, the TSC will consist of an independent chair with clinical and research expertise in psychiatry and psychology and a patient representative. The Committee will meet approximately every 6 months from the start of the trial. The TSC can prematurely close the trial.

The DMEC will consist of an independent statistician and two independent clinicians with clinical trial expertise. The DMEC will agree a charter and can recommend premature closure of the trial to the TSC in accordance with Standard Operating Procedure GOV003.

The TMG will meet at least quarterly during the trial. An intervention development group will meet more frequently during the first phase of the project and involve the DESMOND team and members of the wider study team where relevant.

Trial monitoring procedures, central and site monitoring will be undertaken at a level appropriate to a risk assessment performed by the sponsor or their delegate. Central (remote) monitoring may include documents (e.g. consent forms) being sent to CTRU by post.

Project management

Sheffield Health and Social Care NHS Foundation Trust will act as the sponsor for the trial, and therefore will have overall responsibility for the trial along with the Chief Investigator.

Trial management will be provided by the Clinical Trials Research Unit (CTRU) who adhere to their own Standard Operating Procedures (SOPs). The TMG will include a Trial Manager who will be supervised by the Assistant Director of the Sheffield CTRU and will liaise with the whole study team. The Trial manager will contact the CI and meet with the Assistant Director of the CTRU regularly. The CTRU will work with the DESMOND team to ensure the intervention development study informs the trial including, any amendments to patient information or trial intervention materials required following adaptation of the intervention.

Team expertise

The research team has the expertise to cover all aspects of the research and the right blend of multidisciplinary skills – clinicians, behaviour change specialists, experienced trialists, statisticians and health economists, as well as a patient representative and carer. The team is led by Richard Holt Professor in Diabetes & Endocrinology, University of Southampton. Professor Holt is an international expert on physical health in people with mental illness, including experience of physical health screening & delivery of lifestyle interventions.

11. Data handling and record keeping

Intervention Development Study

Data collected during the IDS will be handled by the University of Leicester Hospitals NHS Trust. Records will be kept in lock filing cabinets and in locked officers. The researchers conducting focus groups will be responsible for both the recording and the storage of the audio recordings. All recordings will be transferred, using encrypted media, to a secure hard drive at the University Hospitals of Leicester until the end of the developmental stage after which they will be destroyed.

Anonymised transcriptions of recordings will be kept for five years on the secure servers at the University Hospitals of Leicester, NHS Trust. Semi-structured interviews with participants in the IDS will be conducted by researchers from The University of Sheffield CTRU. Audio recordings will be stored on secure University of Sheffield servers. Interviews will be transcribed verbatim and the recordings destroyed.

STEPWISE Trial
The CTRU will co-ordinate data collection and follow-up of trial participants in collaboration with the UK centres.

Participant data will be collected and recorded on study-specific case report forms (CRFs) including patient questionnaires and then entered onto a remote web-based data capture system, transferring data to Sheffield CTRU for analysis. Data entry will be completed by trained and authorised individuals at research sites. Participant confidentiality will be respected at all times. Completion of the case report form/s and data entry on to study database will be the responsibility of the PI at each participating centre. Members of the research team at each site are responsible for cleaning the data entered locally, as queries are raised remotely in the data management system.

The data management system uses industry standard techniques to provide security, including password authentication and encryption. Access is controlled by usernames and encrypted passwords, and a comprehensive privilege management feature can be used to ensure that users have access to only the data required to complete their tasks.

The system will have a full electronic audit trail and will be regularly backed up. Quality control procedures will be applied to validate the trial data. Error reports will be generated where data clarification is required. Output for analysis will be generated in a format and at intervals to be agreed between Sheffield CTRU and the Chief Investigator. Trial documents (paper and electronic) will be retained in a secure location during and after the trial has finished in accordance with CTRU SOP PM015 Study Files and Filing.

Archiving
All source documents will be retained for a period of 6 years following the end of the trial by research sites. Each investigator is responsible for ensuring records are retained and securely archived at site during the retention period and information supplied to the Chief Investigator. Where trial related information is documented in the medical records those records will be retained for at least 6 years after the last patient last visit. Access will be restricted to authorised individuals.

Data held by the CTRU will be stored in accordance with the archiving Standard Operating Procedure (CTRU SOP PM012) for 6 years following completion. Archived documents will be logged on a register which will also record items retrieved, by named individuals, from the archive. Electronic data will be stored in an 'archive' area of the secure CTRU server for a minimum of five years to ensure that access is future-proofed against changes in technology. Electronic data may also be stored (e.g. on a compact disc) with the paper files. Archived documents will be transferred to the Sponsor before destruction.

12. Data access and quality assurance

The sponsor will permit monitoring and audits by the relevant authorities, including the Research Ethics Committee. The investigator at each site, in line with responsibilities set out in the Research Governance Framework, will allow monitoring and audits by these bodies, the sponsor and CTRU and provide direct access to source data and documents (in line with CTRU SOP QU001 and SOP DM009) to perform source data verification and data completeness checks. A general check of the continued suitability of the site will also be performed.

The study will use the CTRU's in-house data management system for the capture and storage of participant data. The system stores all data in a PostgreSQL database on virtual servers hosted by Corporate Information and Computing Services (CiCS) at the University of Sheffield. Industry standard techniques are used to provide security, including password

authentication and encryption using SSL/TLS. Access to the system is controlled by usernames and encrypted passwords, and a comprehensive privilege management feature is used to ensure that users have an appropriate level of access to data required to complete their tasks. Personal identifiable data will be stored securely at research sites and separate from data collected on the case report form/s. Data will be anonymised and will only be identifiable by participant ID number, and no patient identifiable data will be transferred from the database to the statistician. Participating sites will enter data from the paper CRF onto the study database.

The data management system provides validation and verification features which will be used by CTRU to monitor study data quality, in line with SOPs and the DMMP. Error reports will be generated where data clarification is required. The investigator will be responsible for validating data collected at their site.

13. Publication

Results of the study will be submitted for publication in peer reviewed journals and for presentation at national and international conferences. Other activities will include dissemination to relevant national charities and Clinical Research Networks.

At a local level, results will be shared with clinicians and commissioners in the participating centres.

The study team are obliged, by the terms of its contract, to notify the National Institute for Health Research Health Technology Assessment (NIHR HTA) Programme of any intention to publish project outputs at least 28 days in advance of publication. This includes journal articles, oral and poster presentations.

14. Finance

STEPWISE is funded by the National Institute for Health Research Health Technology Assessment Programme (project number 12/28/05) and details have been drawn up in a separate agreement/s.

15. Ethical considerations

The ethical issues in this trial will be related to the identification and recruitment of patients, the procedure for gaining fully informed consent, and data protection arrangements.

Written informed consent will be obtained from every participant. Participant information and consent forms were co-written by our service-user and carer representatives. Patients' data collected during the course of the research will be processed in accordance with the Data Protection Act 1998. We will also seek the patient's permission to inform their general practitioner that they are taking part in this study. Documentation relating to trials managed by Sheffield CTRU is retained for at least 5 years after notification of the trial's end.

The project will include people who are detained under the Mental Health Act (most commonly Community Treatment Orders) if they have capacity to give informed consent to inclusion in the trial. If a participant is detained in hospital under the Mental Health Act during the trial, the participant will still be able to attend intervention sessions if they have been permitted a leave of absence under Section 17. The leave of absence would be agreed by a responsible clinician and a member of staff might escort the participant to the session/s.
The intervention development study and trial documentation, including this protocol, has been submitted and given a favourable opinion by South Yorkshire NHS Research Ethics Committee.

Research governance approval will be sought from the NHS Trust participating in the Intervention Development Study. The trial will be submitted for local NHS research governance approval for each participating trust.

16. Indemnity / Compensation / Insurance

This is an NHS sponsored study. For NHS sponsored research HSG (96) 48 reference no. 2 refers. If there is negligent harm during the clinical trial when the NHS body owes a duty of care to the person harmed, NHS Indemnity will cover NHS staff, medical academic staff with honorary contracts and those conducting the trial. NHS Indemnity does not offer no-fault compensation and is unable to agree in advance to pay compensation for non-negligent harm. Ex-gratia payments may be considered in the case of a claim.

The University of Sheffield has in place insurance against liabilities for which it may be legally liable and this cover includes any such liabilities arising out of this research project.

17. References

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