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The NIHR Evaluation, Trials and Studies Coordinating Centre (NETSCC), based at the University of Southampton, manages evaluation research programmes and activities for the NIHR

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Protocol
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Psycho-education with problem solving (PEPS) therapy for adults with personality disorder: A community-based randomised controlled trial

Short Title:	Psycho-education with problem solving therapy for personality disorder
Acronym:	PEPS
ISRCTN:	ISRCTN70660936
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Trial Sponsor:	Nottinghamshire Healthcare NHS Trust
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TRIAL SYNOPSIS

Title	Psycho-education with problem solving (PEPS) therapy for adults with personality disorder: A community-based randomised controlled trial
Acronym	PEPS
Short Title	Psycho-education with problem solving therapy for personality disorder
Chief Investigator	Professor Mary McMurran
Objectives	To evaluate the effectiveness of PEPS therapy compared with treatment as usual in improving social functioning in community based adults with personality disorder.
Trial Configuration	Two-arm, parallel group randomised controlled trial.
Setting	NHS Trusts across the UK providing mental health services.
Sample Size Estimate	To detect a mean difference in Social Functioning Questionnaire score of 2 points with a two-sided significance level of 1% and power of 80% with equal allocation to two arms would require 120 patients in each arm of the trial.
Number of Participants	To allow for 30% drop out 170 participants will be recruited per arm, i.e. 340 in total.
Eligibility Criteria	*Inclusion:* Living in the community (including residential or supported care settings); presence of one or more personality disorder; aged 18 or over; proficiency in spoken English; capacity to provide informed consent. *Exclusion:* Primary diagnosis of major functional psychosis; insufficient degree of literacy, comprehension or attention to be able to engage in trial therapy and assessments; currently engaged in a specific programme of psychological treatment for personality disorder or likely to start such treatment during the trial period; currently enrolled in any other trial.
Description of Interventions	*PEPS therapy:* PEPS therapy consists of up to 4 individual weekly psycho-education sessions, followed by 12 weekly group problem solving therapy sessions with additional, optional fortnightly support sessions. *Treatment as usual:* Treatment as usual will be provided in accordance with usual clinical practice. For the purposes of the trial an advisory minimum standard of treatment as usual will be recommended which will include one care planning session which includes plans for future contact with services and details of alternative sources of support, with a follow-up session after approximately 4 weeks and a further session approximately 4 months later, with additional telephone support.

Duration of Study	The recruitment period is estimated to last approximately 26 months from initiation of the first site to recruitment of the final participant. The duration of participant involvement in the trial will be a maximum of 84 weeks from recruitment to final follow-up.
Randomisation and Blinding	Randomisation will be based on a computer generated pseudo-random code using randomly permuted blocks of randomly varying size. Participants and research team members delivering the interventions will be aware of the treatment allocation. Research Assistants administering the outcome measures will be blinded to treatment allocation.
Outcome Measures	*Primary:* Social functioning at 72 week follow-up assessed by the Social Functioning Questionnaire (SFQ). *Secondary:* Receipt and cost of services; quality of life; depression and anxiety; overall assessment of functioning; clients' assessment of problems; treatment alliance; social problem solving skills.
Statistical Methods	Effectiveness will be assessed using a general linear model with SFQ score as response and terms for treatment arm and relevant covariates including Centre.

ABBREVIATIONS

AE	Adverse Event
CBT	Cognitive Behavioural Therapy
CI	Chief Investigator
CRF	Case Report Form
CSRI	Client Service Receipt Inventory
CTU	Clinical Trials Unit
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders (4th Edition)
EAP	Economic Analysis Plan
EOT	End of Trial
EQ-5D	EuroQoL: European Quality of Life Assessment
GAF	Global Assessment of Functioning
GCP	Good Clinical Practice
HADS	Hospital Anxiety and Depression Scale
ICD	International Classification of Diseases
ICF	Informed Consent Form
IPDE	International Personality Disorder Examination
NHS	National Health Service
NRES	National Research Ethics Service
PEPS	Psycho-education with problem solving therapy
PI	Principal Investigator at a local centre
PIS	Participant Information Sheet
QALY	Quality Adjusted Life Year
REC	Research Ethics Committee
R&D	Research and Development Department
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SFQ	Social Functioning Questionnaire
SOP	Standard Operating Procedure
TMG	Trial Management Group
TSC	Trial Steering Committee

BACKGROUND INFORMATION AND RATIONALE

Personality disorder is one of the most prevalent forms of mental health problem, associated with substantial healthcare costs [1,2,3]. People with personality disorder suffer high levels of distress, suicide, self-harm, addiction, family breakdown, and social exclusion. Despite this, there is little reliable evidence on the effectiveness of treatments for personality disorder. Recent systematic reviews [4,5] have identified only 27 randomised controlled trials (RCTs) with a total of 1731 participants published up to 2006. The majority of studies were underpowered, most had multiple outcome measures, and only one-third measured social functioning, agreed to be the most significant clinical problem for this group of patients.

Good social problem solving is one component of social competence [6,7]. Social problem solving is defined as "the self-directed cognitive-affective-behavioural process by which an individual attempts to identify or discover solutions to specific problems encountered in everyday living" [8, p.11]. There is abundant evidence of an association between social problem-solving deficits and problems related to personality disorders [9,10,11,12]. One study has found that people with personality disorders report less desirable scores on all Social Problem Solving Inventory-Revised (SPSI-R) [13] scales compared to a functional sample of mature students [7]. This information suggests that social problem solving therapy may benefit people with personality disorders.

Problem solving therapy is suited to people with personality disorder because the focus is upon reducing personal distress and improving social functioning, which are considered to be of paramount importance in the treatment of personality disorder [14]. Furthermore, social dysfunction has been empirically identified in several studies as an integral component of personality disorder [15,16,17]. The aim in problem solving therapy is to help people recognise their strengths and limitations and work with these to learn new skills that will enable them to cope more effectively with life's problems. Problem solving therapy works to decrease the person's negative problem orientation and develop positive orientation, without which therapy is unlikely to be effective [18].

Engaging people with personality disorders in treatment is a major challenge [19]. The social problem solving approach enhances engagement by offering an accessible framework for change, supporting people in the experience of successful problem solving and encouraging independence rather than reliance on therapy. Furthermore, psycho-education with problem solving (PEPS) therapy has a preliminary psycho-education component which aims to educate, build rapport, and motivate people for problem solving therapy. Personality disorders and their impact are discussed in a collaborative dialogue and problems that may be worked upon in group sessions are identified.

Recent meta-analyses of problem solving therapy outcome studies document its effectiveness for people with a wide range of mental health problems [18,20,21]. Our own research in this area began with detained personality disordered offenders, who were identified as performing poorly at all aspects of social problem solving compared with offenders with no personality disorder and with non-offenders [22,23]. Our team conducted a pilot study of a psycho-educational intervention aimed at clarifying the personality disorder diagnosis and identifying associated problems which led to an increase in patients' knowledge about personality disorder and improved the therapeutic alliance [24]. We also evaluated brief problem solving therapy with this client group, finding that social problem solving abilities improved and that this improvement was sustained at 6 month follow-up [25].

A combined psycho-education and problem solving (PEPS) therapy was evaluated with community adults with personality disorder in a Phase 2 exploratory trial [26]. Overall, this sample had the lowest social problem solving scores in comparison with mature students, prisoners, and personality disordered offenders [27]. At the end of treatment, compared to a wait-list control group, those treated with PEPS therapy showed better social functioning, as measured by the Social Functioning Questionnaire [28]. Analyses were conducted to examine the hypothesised mechanism of change, namely that improved social problem solving leads to improved social functioning [29]. These analyses indicated that all aspects of social problem solving improved over the course of PEPS therapy, and that, controlling for baseline level of social functioning, the most important predictor of improvement in social functioning was a reduction in negative problem orientation, i.e., people felt less threatened by problems and more confident in their ability to solve problems. This exploratory study has been identified as important in four ways [30,31]. First, the intervention was brief and hence is likely to be more acceptable to patients and services. Second, PEPS therapy was delivered in real clinical settings, hence its likely effectiveness in everyday practice was indicated. Third, PEPS therapy was offered to people with any personality disorder or combination of personality disorders, so it was inclusive rather than exclusive. Fourth, PEPS therapy was delivered by non-specialist staff, hence it would be possible to deliver it relatively cheaply. In addition, a Delphi study of patients' views of PEPS therapy indicated that it was perceived as acceptable and useful [32].

Overall, PEPS therapy has the potential to contribute to the Department of Health's agenda that personality disorder should no longer be a diagnosis that excludes people from services [33]. It is an intervention in which staff can easily be trained, and thus has the potential to make a significant contribution to building workforce capacity [34]. A definitive evaluation needs to be conducted, and there is now sufficient information about PEPS therapy on which to base such a trial [35].

TRIAL PURPOSE AND OBJECTIVES

PURPOSE

The purpose of the trial is to evaluate the effectiveness of PEPS therapy compared with treatment as usual.

PRIMARY OBJECTIVE

To evaluate the effectiveness of PEPS therapy compared with treatment as usual in improving social functioning in community based adults with personality disorder.

SECONDARY OBJECTIVES

- To assess the costs and cost-effectiveness of PEPS therapy compared with treatment as usual.
- To examine the effects on scheduled and unscheduled use of services.

- To examine the process of change by testing the hypotheses a) that psycho-education improves the therapeutic relationship, and b) social problem solving therapy improves social problem solving skills.
- To evaluate referrers' and participants' perceived benefits from the intervention.
- To conduct a qualitative investigation of the application of PEPS in practice to identify the views of service users.

TRIAL DESIGN

CONFIGURATION

A two-arm, parallel group randomised controlled trial comparing the effectiveness of PEPS therapy with treatment as usual for the treatment of adults with personality disorder living in the community and recruited from NHS Trusts providing mental health care within the UK.

PRIMARY ENDPOINT

The primary endpoint is social functioning at 72 week follow-up.

SECONDARY ENDPOINTS

i. Receipt and cost of services post-therapy and at 72 week follow-up.
ii. Scheduled and unscheduled service use post-therapy and at 72 week follow-up.
iii. Quality of life post-therapy and at 72 week follow-up.
iv. Referrer's ratings of functioning post-therapy and at 72 week follow-up.
v. Anxiety and depression post-therapy and at 72 week follow-up.
vi. Client's assessment of problems post-therapy and at 72 week follow-up.
vii. Treatment alliance post psycho-education.
viii. Social problem solving skills post problem solving therapy.

RANDOMISATION AND BLINDING

Randomisation will be based on a computer generated pseudo-random code using random permuted blocks of randomly varying size, created by the Nottingham Clinical Trials Unit (CTU) in accordance with their standard operating procedure (SOP) and held on a secure server. The randomisation will be stratified by recruiting centre and sex. Access to the sequence will be confined to the Trial Data Manager.

The Investigator, or an authorised designee, will access the treatment allocation for each participant by means of a remote, internet-based randomisation system developed and maintained by the Nottingham CTU. The sequence of treatment allocations will be concealed until interventions have all been assigned and recruitment, data collection, and all other trial-related assessments are complete.

Participants and research team members delivering the interventions will be aware of the treatment allocation. Outcome measures will be administered by Research Assistants blinded to treatment allocation in order to reduce assessment bias as far as possible.

Maintenance of randomisation codes and procedures for breaking code

There is no foreseeable situation where Research Assistants would need to know the treatment allocation of a particular participant, and as a result there will be no procedures in place for breaking the randomisation code.

TRIAL MANAGEMENT

Day-to-day management of the trial will be undertaken by the Trial Manager at the Nottingham Clinical Trials Unit (CTU). The CTU will be responsible for managing all aspects of the trial including protocol development, case report form (CRF) creation, database design and maintenance, randomisation, trial management, study monitoring and coordinating the oversight committees. The CTU will ensure that the trial is run in accordance with standard operating procedures (SOPs), the requirements of research governance and the principles of Good Clinical Practice (GCP).

A number of committees will be assembled to ensure the proper management and conduct of the trial, and to uphold the safety and well-being of participants. The general purpose, responsibilities and structures of the committees are described in this protocol. However each committee will develop its own rules and procedures which may evolve with time.

Trial Management Group

The Trial Management Group (TMG) will oversee the operational aspects of the trial. The TMG will meet regularly to review the progress of the trial and address any issues arising.

Trial Steering Committee

The Trial Steering Committee (TSC) will be set up with an independent Chairperson and will monitor, review and supervise the progress of the trial. The independent Trial Steering Committee will monitor *blinded* data to consider safety and efficacy indications. The TSC will recommend discontinuation of the study if significant ethical or safety concerns arise or if there is very clear evidence of benefit (clinical or statistical) prior to completion of the study. The TSC will consider reports from the DMC when making recommendations.

The TSC will meet independently prior to the start of the study and will agree terms of reference.

Data Monitoring Committee

An independent Data Monitoring Committee will be established with access to *unblinded* data to provide independent review and recommendations in the light of potential treatment effect.

The DMC will meet or teleconference prior to the start of the study and will agree terms of reference and a provisional meeting or teleconferencing schedule.

Only the Data Monitoring Committee will have access to unblinded data until the final outcome assessment has been completed.

DURATION OF THE TRIAL

Recruitment Period

The trial recruitment period is estimated to last for approximately 26 months from initiation of the first study site to recruitment of the final participant.

End of the Trial

The end of the trial is defined as the last follow-up visit for the final participant recruited.

SELECTION AND WITHDRAWAL OF PARTICIPANTS

Inclusion Criteria

1. Living in the community (including residential or supported care settings).
2. Presence of one or more personality disorders, as identified by the International Personality Disorder Examination.
3. Aged 18 or over.
4. Proficiency in spoken English. (This is necessary for trial participation because of the requirements of the interventions being used.)
5. Capacity to provide valid informed consent.

Exclusion Criteria

1. A primary diagnosis of major functional psychosis.
2. Insufficient degree of literacy, comprehension or attention to be able to engage in trial therapy and assessments, as assessed by the Investigator or authorised designee in conjunction with the participant's usual care team. This may be a result of psychosis, developmental disability, organic brain disorder, substance use, or any other disorder or disability.
3. Currently engaged in a specific programme of psychological treatment for personality disorder, or likely to start such treatment during the trial period.
4. Already enrolled in any other trial.

Recruitment

Participants will be recruited from selected NHS Trusts providing mental health care. Information about the trial will be on display in waiting rooms, offices etc. The initial approach will be from a member of the potential participant's usual care team (which may include the Investigator) who will ask the potential participant if they are willing for a member of the research team to meet with them and discuss the study.

The Investigator or authorised designee will inform the participant of all aspects pertaining to participation in the study. It will be explained to the potential participant that entry into the trial is entirely voluntary and that their treatment and care will not be affected if they decide not to participate. It will also be explained that they can withdraw at any time.

Informed consent

The process for obtaining informed consent will be in accordance with the REC guidance, and Good Clinical Practice (GCP) and any other regulatory requirements that might be introduced.

The Investigator or an authorised designee will explain the details of the trial and provide a Participant Information Sheet, ensuring that the participant has sufficient time to consider whether or not to take part; in all cases this will be a minimum of 24 hours. The Investigator or an authorised designee will answer any questions that the participant has concerning study participation and ensure that these questions have been answered satisfactorily before consent is obtained.

The Investigator or authorised designee shall emphasise to potential participants that consent regarding study participation may be withdrawn at any time without penalty or affecting the quality or quantity of their future medical care, or loss of benefits to which the participant is otherwise entitled. Participants will be asked to provide consent for the use of data already collected in the event of their early withdrawal from the trial.

All participants will provide a signed and dated Consent Form before they enter the trial and before they undergo any study specific interventions or assessments. One copy of the signed consent form will be kept by the participant, one copy will be filed in the participants' clinical notes and the original signed form will be retained in the Investigator Site File.

Should there be any subsequent amendment to the final protocol, which might affect a participant's involvement in the trial, continuing consent will be obtained using an amended Informed Consent Form which will be signed by the participant. If the Informed Consent Form is amended during the study, the Investigator will follow all applicable regulatory requirements pertaining to approval of the amended Informed Consent Form by the REC and use of the amended form (including for ongoing participants).

Expected duration of trial participation

The duration of involvement in the trial for all participants will be a maximum of 84 weeks from recruitment to the final follow-up visit. This time allows for potential waiting times between recruitment and the initiation of treatment.

Retention

Retention of trial participants will be facilitated by maintaining regular contact throughout the follow-up period. In addition to scheduled follow-up appointments, all participants will be contacted by their preferred means with an update on trial progress approximately eight months after the end of treatment.

Withdrawal of participants from therapy or assessments

Participants may withdraw from any aspect of the trial at any time. Participants are not required to give a reason for withdrawal, but this will be requested and recorded if provided. Individual participants may also be withdrawn from the trial therapy for safety reasons at the discretion of the investigator.

The following withdrawal criteria may apply:

- Adverse events

- Withdrawal of consent
- Development of excluded conditions
- Investigator discretion

Participants will be made aware that withdrawing from the trial therapy will not affect their future care provision, and if they withdraw from the trial arrangements will be made for their care to continue.

Participants withdrawing from trial therapy prematurely will be encouraged to remain in the trial for follow-up, however it will be emphasised that this is voluntary and participants wishing to withdraw entirely from the trial will be free to do so.

TRIAL TREATMENT AND REGIMEN

Following recruitment, screening and baseline assessments participants will be randomised to receive treatment as usual only or treatment as usual plus PEPS therapy which will consist of up to four weekly individual psycho-education sessions followed by twelve weekly group problem solving therapy sessions and additional, optional support sessions. Follow-up assessments for all participants will be completed after the initial treatment phase (weeks 5 – 10), immediately after the second treatment phase (during weeks 24 – 26) and again four months after the end of the intervention and finally 72 weeks post-randomisation. Participants will also be contacted 8 months after the intervention with an update on trial progress, to encourage retention in the trial at 72 week follow-up.

Psycho-education with problem solving (PEPS) therapy

Psycho-education combined with problem solving (PEPS) therapy is a complex cognitive-behavioural intervention that integrates individual and group therapies.

Psycho-education consists of up to 4 sessions of an individual collaborative dialogue designed to build a rapport with patients, inform them about their personality disorder, discuss its effects on interpersonal relationships and social functioning, and enhance motivation for therapy. In psycho-education, participants are taken through their personality disorder diagnoses, as identified via a structured clinical assessment. Participants are asked what problems they experience in relation to their personality disorder and they are then guided to specify problems which are then prioritised to be addressed in the problem solving therapy sessions.

Problem solving therapy is a 12-session group intervention designed to teach people strategies for solving interpersonal problems. Participants are encouraged to learn the process of a) identifying negative feelings and using these as a cue for initiating the problem solving process; b) defining their problem clearly and accurately; c) setting specific goals for change; d) generating solution options; e) considering the consequences of each option; and f) selecting potentially effective options and organising these into a means-end action plan. Participants are then expected to implement the action plan and are offered individual support sessions to help with implementation. Progress with the action plan is reviewed in the next group session.

Throughout the twelve week problem solving therapy group sessions, participants will be offered additional, optional fortnightly individual support sessions with a group facilitator.

Treatment as usual

PEPS therapy will be compared with treatment as usual. This will be provided in accordance with normal clinical practice. For the purposes of the trial an advisory minimum standard of treatment will be recommended which will include an initial care planning session with a mental health worker, including plans for future contact with services and details of alternative sources of help and support, with a follow-up session after approximately 4 weeks and a further session approximately 4 months later with additional telephone support.

MEASURES

Descriptive measures

Data will be collected on the participants' age, sex, ethnicity, socioeconomic status, education level and the route of referral into the study. Risk assessment data regarding the history of risk to self and others will also be collected to help ensure the personal safety of participants and researchers, inform safety reporting and enable comparison of the PEPS sample with the new PD diagnostic criteria being developed in ICD-11.

Screening measures

i. The presence of personality disorder will be confirmed using the International Personality Disorder Examination (IPDE) [36]. The IPDE is a 99-item, semi-structured interview that allows both diagnostic and dimensional scores to be extracted for each personality disorder according to either DSM or ICD criteria. Each item is scored as the behaviour or trait being absent or normal (score 0), exaggerated or accentuated (score 1), or at the criterion level or pathological (score 2).

ii. Adequate literacy is required to engage in trial therapies and assessments. In the majority of cases this will be assessed by the Investigator or authorised designee in conjunction with the participants usual care team. If adequate literacy is unable to be established in this way, a test of literacy will be completed at the screening assessment using the Basic Skills Agency, Fast Track 20 Questions [47].

Primary outcome

The primary outcome is social functioning as measured by the Social Functioning Questionnaire (SFQ) [28]. This is an 8-item self-report scale, each item scored on a scale from 0 to 3. A reduction (i.e. an improvement) of 2 points or more on the SFQ at 72 week follow-up is the specified clinically significant change.

SFQ has been selected because personality pathology manifests primarily as persistent social dysfunction, and the main purpose of therapy is to improve patients' social functioning. The items cover the domains of home, work, leisure, and relationships. Respondents rate the extent to which they have experienced problems in each area over the last two weeks. SFQ scores correlate well with measures of psychiatric distress and are stable over time.

Secondary effectiveness outcomes

i. Scheduled and unscheduled service use (Record Check). Data on mental health service use, Emergency Department attendances and hospital admissions will be collected through a review of mental health service and GP records to ascertain use of scheduled and unscheduled services. Because people with personality disorder are often chaotic users of services we hope to find a reduction in unscheduled service

usage and an increase in scheduled service usage. Service use data will be collected retrospectively for the duration of involvement in the trial, from baseline to 72 week follow-up. The long-term follow up is necessary to pick up potential improvement overall, rather than capture a temporary increase at the end of treatment.

ii. Change in referrer's score on Global Assessment of Functioning (GAF) [40]. This is the standard method for representing a clinician's judgment of a patient's overall level of psychosocial functioning and will be rated by the referrer.

iii. Anxiety and depression (Hospital Anxiety and Depression Scale; HADS) [41]. A reduction in mental distress is an important outcome for service users [14], therefore anxiety and depression will be measured using the HADS.

iv. Client's assessment of problems (i.e., specific treatment targets for individuals) A focus on the problems most relevant to the client is considered important [42]. Participants will be asked to identify their three most important problems and rate their severity before, during and after treatment.

v. Treatment alliance assessed by the Working Alliance Inventory (WAI) [43]. The WAI examines the development of treatment alliance, and will be used to assess the effectiveness of the psycho-education component in developing treatment alliance. The WAI short-form is a 12-item questionnaire that can be administered to both clients and therapists. Each item is rated on a 7-point scale and scores are produced on three factors: the therapeutic bond, the agreement on goals, and the agreement on tasks.

vi. Social problem solving skills assessed by the Social Problem Solving Inventory – Revised (SPSI-R) [13]. The SPSI-R assesses the development of social problem solving skills to examine whether the social problem solving component improves these skills as expected. The SPSI-R is a 25-item client self-report questionnaire that measures problem solving orientation (positive and negative) and problem solving style (rational, impulsive and avoidant).

Measures v and vi are intended as measures of the processes of change.

Health economic outcomes

i. Receipt and cost of services (Client Service Receipt Inventory; CSRI) [38].
This records use of health and social care, criminal justice, informal care services, employment and benefits and will be used to calculate service costs. Service use will be assessed for the period 6 months prior to baseline, and at three points after treatment (immediately after, at 4 months and at 72 weeks post randomisation). The long-term follow up is necessary to pick up potential improvement overall, rather than capture a temporary increase at the end of treatment.

ii. Quality of life (EuroQOL; EQ-5D) [39].
This is a health-related quality of life measure and will be used to generate quality adjusted life years (QALYs) for use in the economic evaluation. The EQ-5D will be administered before and after treatment, and again at 72 weeks post randomisation follow-up.

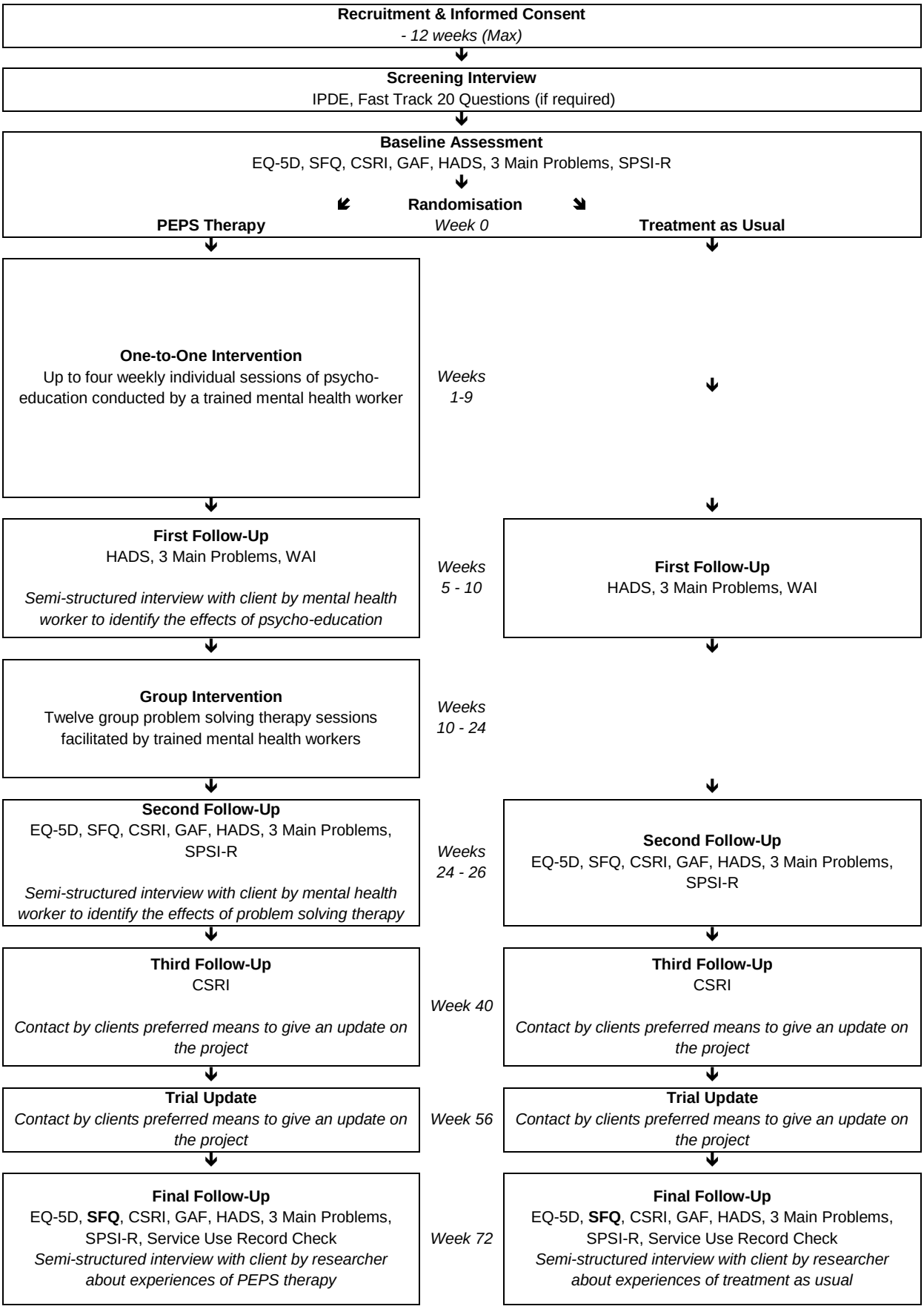
Safety and tolerability measures

Adverse events occurring in trial participants will be recorded and monitored. Premature withdrawal from the trial therapies will also be reported, with reasons for withdrawal documented where these are given.

Process measures

Semi-structured interviews will access information about experiences of therapy, its perceived effects and its perceived limitations. Interviews will also provide an opportunity to support people after psycho-education, since some participants report finding this distressing [32]. This data will be analysed in a separate qualitative analysis, using thematic analysis.

TRIAL FLOW-CHART



COMPLIANCE

Participant attendance

Participants allocated to PEPS therapy will be expected to attend every session, and regular attendance will be encouraged in accordance with normal clinical practice. A record of attendance at sessions will be maintained for all participants. Participants will not be withdrawn from the trial for reasons of poor attendance.

Assessment and Treatment fidelity

Assessment fidelity.

IPDE interviews and scorings will be checked by an external clinician. Audiotapes of at least two early IPDE interviews will be checked. Interviewers who fall below the required competency standard will be given further training and supervision and will be re-assessed.

Treatment fidelity

Treatment fidelity will be assessed in three ways:

i. measuring adherence to protocol implementation (e.g. frequency and duration of treatment sessions);
ii. assessing adherence to therapy as specified in the treatment manual, and
iii. assessing therapist competence.

Adherence to psycho-education will be self-rated by the therapist after the end of all psycho-education sessions, using a standard protocol. In addition to therapist self-ratings, an early sample of audio-taped psycho-education sessions will be rated by an experienced clinician as a post-training competency check.

Adherence to problem solving group sessions will be rated by experienced clinicians, based on a sample of tape-recorded or observed sessions. A number of early group sessions will be rated as a post-training competency check. Ratings of adherence will be made using a standard protocol. Once competence has been established, fidelity will be maintained throughout the trial in regular clinical supervision sessions.

Fidelity checks will be examined at the beginning of the trial to enable us to identify and correct any deviation from prescribed practice. Any issues identified in the course of the trial will be raised in clinical supervision sessions.

Full details of the treatment fidelity monitoring plan will be supplied in a separate document.

CRITERIA FOR TERMINATING TRIAL

The trial as a whole may be stopped because of a change in the opinion of the Research Ethics Committee (REC) or due to issues with trial conduct. In the unlikely event of recurrent adverse events (AEs) the study will be stopped if it is considered that the safety of participants is being put at unacceptable risk. The study may also be stopped in the event of overwhelming evidence of the efficacy, or otherwise, of the intervention which would render continuation of the trial unethical.

Recruitment at a centre may be stopped at the discretion of the Chief Investigator particularly for reasons of low recruitment, protocol violation or inadequate data recording.

STATISTICS

METHODS

Statistical analysis

Demographic and other baseline data will be summarised by descriptive statistics (number [n], mean, standard deviation [SD], median, minimum and maximum) or frequency tables, stratified by treatment.

Measures of compliance will be summarised by descriptive statistics (number [n], mean, standard deviation [SD], median, minimum and maximum) or frequency tables, stratified by treatment arm.

Effectiveness will be assessed using a general linear model with SFQ score as response and terms for treatment arm and relevant covariates including Centre. Analyses will be performed using Stata version 10 or above.

Further details of the statistical analysis will be supplied in the Statistical Analysis Plan, to be finalised in a separate document before data lock.

Economic analysis

The costs of the interventions will be estimated by combining data on number of sessions provided with unit costs. Costs of other services will be calculated by combining service use data collected with the CSRI with appropriate unit costs [e.g. 46]. Costs will be compared between the two groups. Cost-effectiveness will be assessed by combining the cost adapt with outcomes (SFQ and QALYs). Cost-effectiveness will be interpreted using cost-effectiveness acceptability curves.

Further details will be provided in the Economic Analysis Plan, to be finalised in a separate document before data lock.

SAMPLE SIZE AND JUSTIFICATION

A difference of 2 points on the SFQ score is a clinically significant and important difference [44]. We have based our sample size estimate on a conservative (i.e. largest) estimate of SD of 4.53. To detect a mean difference in SFQ score of 2 points with a two-sided significance level of 1% and power of 80% with equal allocation to two arms would require 120 patients in each arm of the trial. To allow for 30% drop out, 170 will be recruited per arm, i.e. 340 in total.

We have considered the need to take clustering effects by therapy group into account. In this study, as in the pilot, participants are individually randomised to the treatment arms, and the observed SD of the response in the intervention arm automatically includes the effect of the clustering by therapist. The analysis may take account of this either by using a

hierarchical model (to allow explicit estimation of the between therapy group variance) or by use of a robust variance estimate.

ASSESSMENT OF EFFECTIVENESS

The primary effectiveness variable will be the SFQ score at 72 week post-randomisation follow-up. The primary effectiveness parameter will be the difference in mean scores between treatment arms.

Secondary effectiveness parameters will be defined similarly for corresponding effectiveness variables (see secondary effectiveness outcomes above).

ASSESSMENT OF SAFETY

No special safety assessments are planned.

PROCEDURES FOR MISSING, UNUSED AND SPURIOUS DATA

Every effort will be made to reduce the proportion of missing data items through trial quality assurance procedures.

Missing covariate and response values will be handled by multiple imputation. In particular the imputation for missing response data at the final assessment will incorporate information on earlier response data and other variables thought likely to account for the missing data.

Once the sets of explanatory variables have been identified, separate data sets will be created for each treatment arm and multiple imputations will be created for each arm after ensuring that the primary response is included in each of the sets of explanatory variables. The multiply-imputed data sets will then be recombined for formal analysis using Rubin's rules.

A sensitivity analysis in which missing outcome data are assumed to be missing not at random will also be performed for the primary outcome and for response.

DEFINITION OF POPULATIONS ANALYSED

Full analysis set: All randomised participants who participated in at least one treatment and for whom at least one post-baseline assessment of the primary endpoint is available.

Safety set: All randomised participants who receive at least one treatment.

Per protocol set: All participants in the full analysis set who are deemed to have no major protocol violations that could interfere with the objectives of the study.

Effectiveness will be assessed on the full analysis set, defined as all randomised participants for whom a post-baseline assessment of the primary endpoint is available, that is, in accordance with the 'intention to treat' (ITT) principle.

Safety summaries will be performed on the safety set.

No per protocol analysis is envisaged therefore no assessment of protocol deviations will be performed.

ADVERSE EVENTS

For the purposes of this trial a recordable adverse event (AE) is defined as any of the following:

- Death for any reason.
- Inpatient hospitalisation for any reason
- Any other serious, unexpected adverse event.

For participants who are randomised to the trial, adverse events will be recorded from consent to trial completion or early withdrawal. For participants who consent but then exit the study before randomisation, adverse events will be recorded from consent until exit from the study.

All clinical and trial staff at each site are responsible for identifying and reporting adverse events. The Principal Investigator at each site is responsible for ensuring that appropriate procedures are in place for recognising and reporting adverse events. This may include asking participants about adverse events during each contact, and asking the participants' clinical team to inform the Principal Investigator if an adverse event is identified. The participants' responsible clinician will be contacted by letter to request information on adverse events throughout the trial.

In the event of loss to follow-up the participants' clinical team and / or GP will be contacted to alert the responsible clinician to the participants' loss to follow-up and to request information on any unreported adverse events to ensure that safety data remains accurate and up to date.

All adverse events should be notified to the trial coordinating centre as soon as site staff become aware of them. Initial notification can be by telephone, but this should be followed up with submission of the Adverse Event form (CRF) by fax or entry onto the eCRF as soon as practically possible, and in all cases within 2 working days.

On receipt, the Chief Investigator will review the adverse event data and determine whether the event is:

- Related: That is, it resulted from administration of any of the research procedures; and
- Unexpected: That is, the type of event is not listed in the protocol as an expected occurrence.

An Adverse Event that is deemed to be both related to the research procedures and unexpected is defined as a Serious Adverse Event (SAE). Reports of Serious Adverse Events (SAEs) will be submitted to the Research Ethics Committee within 15 days of the Chief Investigator becoming aware of the event. The Data Monitoring and Ethics Committee and Trial Steering Committee will also be notified of Serious Adverse Events.

All adverse events will be reported to the Research Ethics Committee, Data Monitoring and Ethics Committee and the Trial Steering Committee as part of the regular reporting requirements. The Chief Investigator shall be responsible for adverse event reporting.

ETHICAL AND REGULATORY ASPECTS

ETHICS COMMITTEE AND REGULATORY APPROVALS

The trial will not be initiated before the protocol, informed consent forms, participant information sheets and other required documents have received approval from the Research Ethics Committee (REC) and the respective National Health Service (NHS) Research & Development (R&D) departments. Should a protocol amendment be made that requires REC approval, the changes in the protocol will not be instituted until the amendment and revised documents (if appropriate) have been reviewed and received approval from the REC and R&D departments. A protocol amendment intended to eliminate an apparent immediate hazard to participants may be implemented immediately providing that the REC are notified as soon as possible and an approval is requested. Minor protocol amendments only for logistical or administrative changes may be implemented immediately and the REC will be informed.

The trial will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki, 1996; the principles of Good Clinical Practice, and the Department of Health Research Governance Framework for Health and Social care, 2005.

RECORDS

Case Report Forms

Case Report Forms (CRFs) are used to record clinical trial data and are an integral part of the trial and subsequent reports. It is therefore essential that CRFs are completed accurately and entries are legible.

The trial will utilise an online data management system (the eCRF) which will serve as the primary record of data for the trial. The eCRF will be provided by the Nottingham Clinical Trials Unit (CTU) in accordance with the CTU Standard Operating Procedures (SOPs). The eCRF stores data on a secure dedicated server. Access is restricted to authorised personnel through individual, password protected accounts.

Optional paper CRF worksheets will also be provided to sites to aid with data collection. All paper CRF worksheet entries will be transcribed to the online eCRF, and any changes on the paper CRF must also be made online. All paper forms will be filled in using black ballpoint pen. Errors shall be crossed out with a single line but not obliterated. Correction fluid must not be used. Corrections to entries will be initialled and dated and a brief explanation of the reason for the change will be recorded if necessary.

Completion of, and access to the eCRF and CRF worksheets will be restricted to those authorised trial personnel approved by the Chief or local Principal Investigator and recorded on the 'Trial Delegation Log'. All trial documents will be treated confidentially and

held securely in accordance with regulations. The Investigator will sign a declaration ensuring the accuracy of the data recorded in the eCRF and worksheets.

At registration each participant will be assigned a trial identification number for use on trial documents and the electronic database. The documents and database will also use the participants' initials (of first and last names separated by a hyphen or a middle name initial when available) and date of birth.

The investigator will make a separate confidential record of the participant's name, date of birth, local hospital number or NHS number, and Participant Trial Number (the Trial Recruitment Log), to permit identification of all participants enrolled in the trial, in case additional follow-up is required.

Only trial staff as listed on the Delegation Log shall have access to trial documentation other than the regulatory requirements listed below.

Source data

Source documents provide evidence for the existence of the participant and permit verification of the data collected. Source documents include, but are not limited to, consent forms, current clinical records and original, completed questionnaires. A CRF may also completely serve as its own source data.

Direct access to source data

The CRF and all source documents shall be made available at all times for review by the Chief Investigator or authorised designee, Sponsor's designee and inspection by relevant regulatory authorities.

DATA PROTECTION

All trial staff and investigators will endeavour to protect the rights of trial participants to privacy and informed consent, and will adhere to the Data Protection Act, 1998. The CRF will only collect the minimum required information for the purposes of the trial. CRFs will be held securely, in a locked room, or locked cupboard or cabinet. Access to the information will be limited to the trial staff and investigators and relevant regulatory authorities (see above). Computer held data including the trial database will be held securely and password protected. All data will be stored on a secure dedicated web server. Access will be restricted by user identifiers and passwords (encrypted using a one way encryption method).

Information about the trial in the participant's clinical notes will be treated confidentially in the same way as all other confidential medical information.

Electronic data will be backed up every 24 hours to both local and remote media in encrypted format.

QUALITY ASSURANCE & AUDIT

INSURANCE AND INDEMNITY

Insurance and indemnity for trial participants and trial staff is covered within the NHS Indemnity Arrangements for clinical negligence claims in the NHS, issued under cover of HSG (96)48. There are no special compensation arrangements, but trial participants may have recourse through the NHS complaints procedures.

TRIAL CONDUCT

Trial conduct will be monitored in accordance with the trial monitoring plan. Monitoring will include systems audit of the Trial Master File for inclusion of essential documents; permissions to conduct the trial; Trial Delegation Log; CVs of trial staff and training received; local document control procedures; consent procedures and recruitment logs; adherence to procedures defined in the protocol (e.g. inclusion / exclusion criteria, correct randomisation, timeliness of visits); adverse event recording and reporting. The Trial Manager, or where required, a nominated designee of the Sponsor, will carry out a site systems audit at least yearly and an audit report will be provided to the Trial Steering Committee.

TRIAL DATA

Monitoring of trial data will include confirmation of informed consent; source data verification; data storage and data transfer procedures; local quality control checks and procedures, back-up and disaster recovery of any local databases and validation of data manipulation. The Trial Manager, or where required, a nominated designee of the Sponsor, shall carry out trial data monitoring in accordance with the trial monitoring plan.

Trial data will be verified by inspection against the source data. A sample of CRFs will be checked for verification of entries made, in accordance with the Trial Monitoring Plan. Where corrections are required these will carry a full audit trail and justification.

Trial data and evidence of monitoring and systems audits will be made available for inspection by the REC as required.

RECORD RETENTION AND ARCHIVING

In compliance with the ICH/GCP guidelines and applicable regulations the Chief or local Principal Investigator will maintain all records and documents regarding the conduct of the study. These will be retained for at least 5 years or for longer if required. If the responsible investigator is no longer able to maintain the study records, a second person will be nominated to take over this responsibility.

The Trial Master File and trial documents held by the Chief Investigator on behalf of the Sponsor shall be finally archived at secure archive facilities. This archive shall include all trial databases and associated meta-data encryption codes.

DISCONTINUATION OF THE TRIAL BY THE SPONSOR

The Sponsor reserves the right to discontinue this trial at any time for failure to meet expected enrolment goals, for safety or any other administrative reasons. The Sponsor shall take advice from the Trial Steering Committee as appropriate in making this decision.

STATEMENT OF CONFIDENTIALITY

Individual participant clinical information obtained as a result of this study is considered confidential and disclosure to third parties is prohibited with the exceptions noted above.
Participant confidentiality will be further ensured by utilising identification code numbers to correspond to treatment data in the computer files.

Clinical information may be given to the participant's clinical team and all appropriate personnel responsible for the participant's welfare.

Data generated as a result of this trial will be available for inspection on request by the Chief Investigator or authorised designee, participating Investigators, representatives of the sponsor, the REC, local R&D Departments and the regulatory authorities.

PUBLICATION AND DISSEMINATION POLICY

PUBLICATION COMMITTEE

The Publication Committee (PC) will be set up by the Trial Management Group (TMG) with the approval of the Trial Steering Committee (TSC) and will comprise the TMG and the TSC Chair, in accordance with the Consolidated Standards of Reporting Trials (CONSORT) Guidance.

PUBLICATION POLICY

The publication policy for this study will cover publications involving results from this study. The purpose is to:

- Facilitate the production of timely, high quality abstracts, slides and manuscripts.
- Avoid inconsistencies and redundancies in the presentation of results from the trial.
- Protect against premature publication and other potential violations of the scientific integrity of the data.
- Provide the opportunity for all investigators to participate in, and receive publication credit for, the presentation of the study's data and results.
- Provide authorship guidelines.
- Protect intellectual property rights which may arise out of this study.

The policy will be administered by the Publication Committee**.**
No unpublished pooled data from any source (e.g. progress reports, reports at annual meetings) can be published in any format without approval of the Publication Committee.

Negative or neutral results will not constitute a reasonable justification to delay publication.

The Publication Committee has overall responsibility for acceptance of projects and final approval of publications, but may delegate responsibilities for specific projects to ad hoc Publications Sub-Committees as required.

DISSEMINATION

The results of the trial will be disseminated through seminars, conferences, professional publications and academic publications by members of the research team.

The results will also be publicly available through publication on the Personality Disorder Institute (PDI) website and the trial website. Dissemination to service users will be facilitated through the trial newsletter, local media and the Mental Health Research Network.

SERVICE-USER INVOLVEMENT

The project team includes two service-user representatives as project collaborators. The service-user representatives commented on the development of the proposal, and will be invited to comment at all stages of the project throughout the planning, implementation, reporting and dissemination. The Trial Steering Committee will include a service user representative to support the management and oversight of the trial. Additional service-user input will be facilitated through the Mental Health Research Network as appropriate.

STUDY FINANCES

FUNDING SOURCE

This study is funded by the Health Technology Assessment programme (HTA) of the National Institute for Health Research (NIHR).

PARTICIPANT STIPENDS AND PAYMENTS

Participants reaching the final follow-up will be offered a non-contingent voucher payment in recognition of their contribution to the trial. Participants will be advised of this in a letter sent before the final follow-up is due. Contact with the participant at the final follow-up will be sufficient for provision of the voucher, i.e. payment is not contingent on completion of the final follow-up assessments.

Reimbursement of travel expenses incurred in relation to attendance at research appointments will be offered. Expense claims and payments will be handled in accordance with local Trust policies and procedures.

Travel expenses incurred by participants in conjunction with the treatments provided in the trial will be paid in accordance with normal clinical practice at the local sites.

SIGNATURE PAGES

Chief Investigator

Name: _____

Signature: _____

Date: _____

Principal Investigator

Name: _____

Signature: _____

Date: _____

Trial Statistician

Name: _____

Signature: _____

Date: _____

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