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Effectiveness and Cost-Effectiveness of Body Psychotherapy in the Treatment of Negative Symptoms of Schizophrenia – A Multi-Centre Randomised Controlled Trial

Introduction

Despite improvements of antipsychotic treatment, schizophrenia patients often experience persistent symptoms and full remissions are infrequent. Patients often do not adhere to existing pharmacological and psychological treatments, and even when they do, currently available treatments have an only limited effect. This applies in particular to negative symptoms which are frequently associated with poor long term outcome.

NICE recently reviewed the literature on the treatment of negative symptoms and identified six trials using different forms of 'arts therapies'. Arts therapies is an umbrella term including different forms of therapies that have central non-verbal components. In the review, NICE explicitly refers to Body Psychotherapy (BPT) as one type of arts therapies and an exploratory trial in the UK (1). NICE "found consistent evidence that arts therapies are effective in reducing negative symptoms as compared to any other control. There was some evidence that the medium to large effect sizes were sustained at up to six months follow up" (2) (p198). The guideline development group (GDG) recognise that at present, the evidence for arts therapies in the treatment of negative symptoms is better than for any other form of pharmacological and psychological intervention. "Consequently the GDG recommend that further large-scale investigations of arts therapies should be undertaken to increase the current evidence base" (2) (p199). In particular, "an adequately powered trial should be conducted to investigate the clinical and cost-effectiveness of arts therapies as compared to an active control in people with schizophrenia" (2) (p200).

BPT refers back to a long tradition in psychiatry. A first trial in schizophrenia patients was published in 1965 showing a significant improvement of the treatment group, as compared to controls, in affective contact, motility and general functioning (3). Four further controlled studies - three of them randomized - compared forms of BPT with non-specific attention, music therapy or fitness training. The results suggest favourable effects of the experimental treatments on a range of outcome variables, including some indicators of negative symptoms (3-6). However, all these studies, which were exclusively conducted before 1980, have serious methodological shortcomings such as small sample sizes, vaguely defined outcome criteria, no systematic assessment of psychopathology, no recording of medication, and no intention-to-treat analysis.

A more recent exploratory randomised controlled trial tested manualised BPT in out-patients with persistent negative symptoms of schizophrenia (1). As compared to a control group receiving supportive counselling, patients in the experimental group showed a significant improvement of negative symptoms. The effect size was large and maintained at a 4 month follow up. The study was considered relevant by NICE (see above), but did not provide sufficient evidence for the clinical and cost-effectiveness of BPT. The major limitations of that study were:

- It was a small exploratory trial on only one site.
- There was only one therapist administering BPT in all groups.
- The control condition was supportive counselling which turned out to be unattractive to many patients so that attendance rates were much lower in the control group than in the experimental group.
- Supportive counselling does not involve physical activity as BPT does. Whilst this does not affect the finding that BPT was associated with a benefit for the patients, the specificity of the effect remains unclear since the control condition did not fully control for the non-specific effects of physical activity and group experience as well as therapist attention.

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To date, there have been no other rigorous trials on BPT or a similar method in the treatment of schizophrenia. The recent Cochrane Review on Dance Therapy in schizophrenia identified the above trial as the only one (7). The authors concluded that "funders of research may wish to encourage future work to increase high-quality evidence in this area" (8). All trials other than the above considered by NICE in their recommendations for arts therapies in schizophrenia used conventional art therapy or music therapy, but no body related modality.

As recommended by NICE a larger pragmatic multi-centre trial with an appropriate active control is now required to provide more substantial evidence on the clinical and cost-effectiveness of BPT in the treatment of negative symptoms of schizophrenia.

The theoretical basis for the effectiveness of BPT vs. an active control group with physical activity refers to three different models of mechanisms. They are not mutually exclusive, and to some extent capture similar processes from different conceptual angles:

A) Enhancing body and self-experience: Since the term schizophrenia was coined by Bleuler, abnormal body experiences were regularly seen as a central part of schizophrenia in phenomenological accounts of the disorder (9). Such experiences featured prominently in descriptions of the experience of patients with schizophrenia (mainly in Swiss and German psychiatry), and played a major role in the concept of ego-psychopathology and disturbed self-experiences as described by Scharfetter (10;11). Empirical studies provide evidence that schizophrenia patients tend to have misperceptions of their body and altered body experience (e.g. in the form of disturbed body schema/perception and body image). Motor acts as performed in BPT may activate somato-sensory circuits important for the foundation of integrated self-experiences and the construction of a coherent ego-structure (12). A therapeutic method that focuses on the patients' perceptions and experiences of their body and its movements may be an effective way of addressing core symptoms (particularly negative symptoms which Bleuler regarded as fundamental and more important for the diagnosis of schizophrenia than the positive symptoms) with a subsequent positive impact on wider experiences and behaviour.

B) Facilitating emotional interactions: BPT is a non-verbal method using body movements as well as creative and enjoyable activities in groups. This makes BPT particularly acceptable and appealing to many patients with schizophrenia who struggle to engage in verbal groups and/or conventional art activities. BPT can be expected to enable such patients to engage in helpful emotional interactions and experiences in a group, and facilitate the responsiveness to interventions by the therapist. This model follows the principles of socio-therapy as they have been outlined in the psychiatric literature since the 1950s (13), but rarely been evaluated in systematic research. Based on this model, BPT uses a focus on movement and body experience as a specific method to facilitate non-specific emotional and activating group interactions which impact on negative symptoms.

C) Linking movement and emotion: Schizophrenia patients tend to have difficulties in emotional information processing (14;15) and display a range of motor abnormalities (16). A link between these phenomena has been suggested in the literature. Trimble (17) outlined that "the regions of the brain that modulate emotion and motivation, have direct access to the brain's motor systems, down as far as the brainstem and beyond, to the neurons that control somatic and autonomic muscular activity" (p49). BPT utilises the link between movement and emotional experience, e.g. when patients test their own movements related to emotions. The concept of mirror neurons may explain why the resulting emotional learning can be enhanced by the group experience when patients observe and imitate expressive movements in other patients.

Based on these three models, the specific components of BPT are A) the focus on body experience, B) the facilitation of emotional group interactions, and C) the link between movement and emotion.
At the same time, physical activity alone and non-emotional group interactions (which occur in BPT as well) without the added therapeutic elements are supposed not to be therapeutic and can therefore be used to define an active control, i.e. a 'sham' condition as required by NICE.

The manual for BPT, which was applied in the exploratory trial and will also be used in the proposed pragmatic trial, intends to utilise the three specific mechanisms.

Beyond the expected clinical effectiveness there are three characteristics of BPT that make it particularly beneficial for rolling out in the NHS:
1) as a group based method, BPT is relatively inexpensive;
2) BPT can be flexibly combined with other treatment methods including all pharmacological interventions;
3) because BPT is so distinct from conventional treatment methods, it can appeal to patients who are difficult to engage in other forms of treatment. The latter point is underlined by findings of a qualitative evaluation of the exploratory trial (unpublished material) in which patients expressed surprise at the multi-faceted approach of BPT and fed back most positively about both its focus and methods.

Planned investigation

Research objectives
The overall objective is to improve the treatment of negative symptoms of patients with schizophrenia through testing a novel treatment method. Following a successful exploratory trial of manualised, group based Body Psychotherapy (BPT), the proposed research will test the clinical and cost-effectiveness of BPT in a pragmatic multi-centre trial. BPT will be administered to schizophrenia patients with a significant level of negative symptoms and compared with an active control condition of Physical Activities (pilates exercises) in groups (PA).

The specific objectives of the trial are:

1. To test the effectiveness of manualised and group based BPT on reducing negative symptoms (primary outcome) in patients with schizophrenia as compared to an active control (both conditions in addition to treatment as usual).
2. To test the effectiveness of BPT on general psychopathology, quality of life, treatment satisfaction, daily activities, emotional response and objective social situation (secondary outcomes) in patients with negative symptoms of schizophrenia as compared to an active control.
3. To test whether effects on primary and secondary outcomes hold true at a six month follow-up period.
4. To assess the cost-impact, cost-effectiveness and cost-utility of BPT.

Research Methods
In a randomised controlled trial, schizophrenia patients with negative symptoms will be randomly allocated to groups for BPT or Physical Activity (PA) as an active control. Both conditions are in addition to treatment as usual and will be delivered in groups of 8 patients each. There will be 3 data collection points, i.e. before treatment, after the 10 week treatment period, and after a 6 month follow-up period. At each of four study sites experimental and control groups will be delivered by two different therapists, and will be assisted by a

volunteer. Outcomes will be analysed on the level of individual patients. The effect of clustering of patients being treated at the same site, by the same therapists and within the same treatment groups will be controlled for in a mixed effects model. The trial cannot be fully "blind" because clinicians and patients cannot be masked towards the allocation of the patients to the experimental or control group. However, researchers will be masked towards the allocation of patients when assessing eligibility and baseline scores (which are pre-randomisation) and outcomes at the end of treatment and after the follow-up period and we will try and maintain "blinding" of the participant's care coordinator.

At each site, the study will be presented and explained to clinicians involving the leads at each site (Priebe, Wykes, Bentall, Lauber) and research assistants. Consultant psychiatrists and team managers will be asked to identify eligible patients in community mental health teams, out-patient clinics, rehabilitation teams, early intervention teams, and assertive outreach teams. Clinicians will then ask patients for consent to be approached by a research assistant. Research assistants will contact patients, explain the study, obtain written informed consent, and establish all inclusion criteria. After the recruitment of 16 patients at one site, research assistants will have another meeting with patients, located either at the NHS site or in the community (which includes the patients' home), in order to complete the baseline assessment. After this assessment the patients will then be randomly allocated to the intervention or control group.

The random allocation will be done by the Pragmatic Clinical Trials Unit (PCTU) at Barts and the London School of Medicine and Dentistry. After allocation, the names and contact details of the patients will be passed onto the clinicians running the groups for BPT and the PA control groups. This will be done through the trial manager at the co-ordinating centre and not the research assistants at the four sites so that the research assistants can maintain masking for interviews at the end of treatment and after the follow up period. The direct communication between the central trial manager and local clinicians at four sites will be prepared. Although it requires good communication between the coordinating centre and up to eight clinicians at four sites, it should be feasible since the time of the allocation can be anticipated (no 'on the spot' randomisation) and the clinicians running BPT and the active control groups are familiar with the requirements of the trial (all of them will have received at least one day of specific training for the trial).

BPT and PA control groups will each run for 10 weeks. After the 10 week intervention period and after a further 6 month follow-up patients will be interviewed by the researchers and outcomes will be assessed. These assessments will be conducted either on NHS sites or in the community, including the patients' home. Ideally, the assessment location will remain the same for each patient at each time-point (i.e. all 3 conducted either in the community or on NHS premises).

Planned interventions

Patients in the experimental group will receive BPT which will be delivered in groups of 8 patients and 20 sessions over a 10 week period. Each session will take 90 minutes. BPT is manualised with the following components:
1) overcoming communication barriers through non-verbal techniques;
2) re-focussing cognitive and emotional awareness towards the body (physical reality, coordination and orientation);
3) stimulating activity and emotional responsiveness,;
4) exploring physical potentials;
5) focussing on strength and experiencing the body as a source of creativity, reliability, pleasure and self-expression;

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6) modifying dysfunctional self-perception and addressing body-related psychopathological features such as boundary loss, somatic depersonalisation, and body schema disturbances.

BPT sessions contain five sections: a) opening circle, describe feelings and energy level; b) warm-up section standing in a circle and warm up using different body parts and movements; c) structured task section, mirroring each other's movements, creating body image sculpture in partners; d) creative movements, group mirroring, creating group sculptures, reflecting on perceptions and emotions; e) closing circle, reflecting on group experience, refocusing on self with body oriented exercises such as self touch, verbal integration (for more details see manual (18)).

All therapists will be accredited dance-movement psychotherapists and receive an additional training in applying the manual of body psychotherapy for patients with negative symptoms of schizophrenia as it was used in the exploratory trial (1). All therapists will receive a three day training at the beginning of the trial and a one day refresher training after each therapist has completed one group (i.e. after completion of two groups at each site). Regular supervision will be provided 3 times within each 10 week treatment period and arranged as a combination of live supervision and web-based conferences. Training and supervision will be provided by the therapist who acted as the therapist in the original exploratory trial (Nina Papadopoulos, who has confirmed her willingness to take this role in the trial and with whom the details of the training and supervision arrangements have been agreed).
Adherence to the manual will be assessed by the author of the manual (Röhricht, who is a co-applicant) based on videotapes of the sessions. He will assess 20% of all sessions and develop a scale to quantify the adherence ratings.

The active control condition of physical activities (PA) will be delivered with the same frequency and length of sessions and overall duration as BPT, i.e. there will be two sessions per week over a ten week period and each session will last up to 90 minutes. PA will be described to patients as a fitness and physical health intervention so that in the recruitment process patients consent to participate in one of two interventions that share several elements, most importantly the format and physical activities. This is intended to limit the risk of different acceptance rates of the two interventions once patients are informed about their allocation.
The venue for the PA groups will be similar rooms as those used for BPT (usually they will be the same rooms, and will be based either on NHS sites, or in facilities hired locally).
PA will consist of pilates exercises and follow the established guidelines for such groups. It will be delivered by pilates trainers.

A brief manual for the pilates groups will be written and contain instructions for how to run the groups as well as references to material describing the exercises in detail.

When tested in previous studies, physical exercises alone had no impact on symptoms of schizophrenia (19). Group interactions will occur as they commonly do when patients are together, but the therapist will not actively encourage or structure them. Therapists will pay attention to patients and respond to them without addressing or verbalising emotions. As an active control condition in this trial, PA will therefore provide moderate physical activity, therapist attention and non-emotional group interaction, but not the specific components of BPT (i.e. a focus on body experience, the facilitation of emotional group interactions, and linking movement and emotional experience).

All pilates trainers will receive an initial training and two supervision sessions within each 10 week treatment period, one of which will be organised as a web-based conference.

Planned inclusion/exclusion criteria

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The inclusion criteria are:

- Aged between 18 and 65 years
- An established diagnoses of schizophrenia according to DSM-IV
- Having had symptoms of schizophrenia for at least 6 months
- Scores of >18 on the subscale negative symptoms of the positive/negative symptom scale (PANSS)
- No change in anti-psychotic medication for 6 weeks prior to recruitment, although dosage may change
- Willingness to participate in groups for BPT or physical activity
- Ability to give written informed consent

The exclusion criteria are:

- Severe physical disability preventing patients from participating in groups for BPT or PA
- Insufficient command of English so that outcomes cannot be reasonably assessed in English
- A physical condition that makes participation in either BPT or the PA control group impossible or potentially harmful

Ethical arrangements
All patients participating in the trial will receive group based treatment in addition to treatment as usual, and treatment as usual will not be compromised for any patient at any point of time. Patients receiving BPT are - on a group level – supposed to benefit from treatment, since patients in the exploratory trial experienced a significant reduction of negative symptoms. Patients in the control group might still benefit from non-specific attention, physical activities and group interactions, but we hypothesise that such benefits will be less substantial than those in the experimental group.

The risks in either group appear limited. There has been some speculation as to whether emotional stimulation as it can occur in BPT might trigger an exacerbation of positive symptoms in patients with schizophrenia. The exploratory trial did not provide any evidence for such a possibility. In any case, all therapists are qualified to detect exacerbations of symptoms during the sessions. Patients will be monitored by their clinicians as part of treatment as usual, and the participation in either group can be terminated at any time if clinicians think there a risk in further participating.

Participation in either group will involve some physical activity which might increase the risk of contracting injuries. However, there is a wide consensus that physical activity overall is rather beneficial for health and that these benefits outweigh the risk of injuries.

The study protocol will be submitted to a MREC. The research team do not anticipate major ethical concerns that would require amendments of the study plan.

Obtaining informed consent from participants
All patients will first be approached by a clinician asking for patient's consent to be contacted by a researcher. Once the patients have consented, they will be contacted by the researcher, fully informed about the study and asked for written informed consent. Consent can be withdrawn at any time without any negative consequences (other than that patients would not have the potential benefits of further participation in the groups on BPT or PA).

We will obtain written informed consent from participants for the pre and post intervention PANSS interviews to be video recorded to enable independent researcher ratings as well as further analysis of the data. This is optional for patients and if they do not wish to be video-recorded, this will not impact on their participation in the study.

Proposed outcome measures
The primary outcome criterion for the effectiveness of BPT is the level of negative symptoms as assessed on the Positive and Negative Symptom Scale of Schizophrenia (PANSS).
Secondary outcomes are:

- the levels of general psychopathology and positive symptoms (also on the PANSS (20)),
- subjective quality of life (Manchester Short Assessment of Quality of Life (21)),
- Activities (5 items from the Time Use Survey (22))
- treatment satisfaction (Client Satisfaction Questionnaire (23)),
- the objective social situation (SIX (24), which combines objective indicators of independent accommodation, employment and having a partner/friend).
- extrapyramidal symptoms (Simpson-Angus Scale (25))
- Emotional experience & Expression (Clinical Assessment Interview for Negative Symptoms – CAINS (26))
- nonverbal communication/gesture behaviour (NEUROGES-ELAN (27))
- Depression (Calgary scale (28))
- Social Functioning (4 items from the Social Network Scale (29))

All criteria will be obtained at pre-treatment baseline, at the end of treatment, and after a 6 month follow-up. Our primary hypothesis relates to endpoints at the end of treatment.

The number of therapy sessions attended by patients in both groups will be recorded. Costs of BPT and the active control will be calculated taking into account the staff time involved in delivering therapy, training received and supervision (including time of both therapists and those providing training/supervision). The training costs will be apportioned over the period of time in the trial during which therapy is delivered. However, the benefits of training are likely to run beyond the trial and therefore sensitivity analyses will involve apportioning training costs over longer periods. Other service use information (including health and social care inputs, medication and informal care) will be collected for the 6 months prior to treatment, the treatment period of 10 weeks, and the 6 month follow-up period using the Client Service Receipt Inventory (30), which has been used in over 200 mental health studies. Service use data will be combined with nationally applicable unit costs (e.g. PSSRU unit costs for community services, BNF for medication, and Reference Costs for hospital care). Informal care costs will be based on the unit cost of a homecare worker, with wage rates for employed carers used as an alternative in sensitivity analyses. Costs will be reported taking an NHS/PSS perspective (in line with NICE guidance). Subsequent analyses will include other services (e.g. criminal justice and informal care). Quality of life adjusted years (QALYs) will be estimated using the EQ-5D (31). QALY gains will be estimated using area-under-curve methods. To assess whether this is sensitive to change in patients with schizophrenia, Spearman's correlations will be used to estimate the relationship between QALY gains and changes in PANSS scores.

Statistical analysis
Our primary analysis will be a strict intention to treat analysis or an available case analysis following intention to treat principles. Which analysis is used will depend on the number of missing values, the validity of any necessary assumptions (which may be particularly uncertain in this case) and the ease of multiple imputation (which will be used for the intention to treat analysis) given the analysis model. Currently, multiple imputation is, for example, much less straightforward if we opt for generalised estimating equations as our

model of analysis. A decision about strict intention to treat or available case analysis will be made and written into a full analysis plan before any analysis is undertaken and before data are unblinded.

We intend to use generalised linear models as appropriate to the outcome, with fixed effects for the intervention and centre and random effects for therapists and therapy groups. If the clustering at one of these levels is having a negligible impact on the precision of results we may use just one level of clustering for simplicity. At end of treatment we expect missing data to be minimal (see later section on sample size calculation). We will use sensitivity analyses to explore the impact of missing data.

We will try and minimise loss to follow-up in both arms through a number of measures. However, differential drop-out is possible. If it does occur, it can occur in two possible ways.

First, it is possible for individuals to drop out of treatment but still agree to have their data collected. If, as suggested by one reviewer, there are more drop-outs of this type from the active control group than from the intervention group (and subsequently many patients in the control group have only treatment as usual with no additional active intervention), the effect that we wish to measure (intervention versus active control) may be overestimated. We will therefore also conduct, as a secondary analysis, a per-protocol analysis. If the conclusions from the two analyses differ, the intention to treat (or available case) analysis will be regarded as the primary analysis, as already stated, and the results of the per-protocol analysis will be discussed and interpreted appropriately.

Second, individuals can drop out of treatment and also be lost to follow up. In this case some assumptions must be made about their outcome data. It is not clear at this stage what the most plausible assumptions are. One may argue that patients are more likely to drop out if they do not feel any benefit from the intervention, so that drop outs are more likely to have ended with a less favourable outcome if they had stayed in treatment. Yet, this is not necessarily so for patients with severe negative symptoms of schizophrenia. They might also tend to drop out when they feel improvement and no further need to attend treatment sessions (in which case drop outs would have ended with more favourable outcomes). Thus, we will also conduct sensitivity analyses, assuming either that those who are lost to follow up would have no improvement as result of any intervention, or that they would have had the maximum improvement seen in participants in the intervention group they have been assigned to. We will conduct sensitivity analyses using the same assumptions in both intervention groups and then opposite assumptions in each of the intervention groups.

A detailed Statistical Analysis Plan will be agreed by the Trial Steering Committee prior to the analysis of unblinded data.

Economic evaluation

Cost data are frequently skewed and so comparisons between the groups will be made using a bootstrap regression model (using 10,000 repetitions). Either bias-corrected or percentile 95% confidence intervals will be reported depending on the level of bias in the data. Cost-effectiveness and cost-utility will be established by combining the cost data (NHS/PSS and then all services) with change scores on the PANSS and QALYs respectively. If BPT or the active control result in lower costs and better outcomes, then it will be 'dominant'. If either group produces better outcomes and a higher cost we will produce incremental cost-effectiveness ratios and explore uncertainty around these by conducting bootstrapped regression analyses with cost and outcome used in turn as dependent variables and the group variable as the independent variable. 1000 cost-outcome combinations will be obtained and these will be plotted on a cost-effectiveness plane. This will enable us to estimate the probability that the intervention is more expensive and more effective, more expensive and

less effective, less expensive and more effective, and less expensive and less effective. In addition, cost-effectiveness acceptability curves (CEACs) will show the probability that BPT or the active control is cost-effective for different values placed on unit-changes in outcome. The net benefit approach will be used (i.e. the monetary value of outcome change minus the service cost) and net benefit will then be used in bootstrapped regression models. The proportion of coefficients for each resample that are above zero will indicate the probability that BPT is the most cost-effective option. The values used for the CEAC based on QALY gains will be £0 to £100,000 in £5,000 increments this range includes the threshold of £20,000 to £30,000 used by NICE). There are few data to inform the choice of values for a CEAC based on PANSS scores. We will therefore choose values which allow us to determine the point at which CEAC 'flattens' (values above this point will have limited importance). We will also report values for PANSS improvements that are linked to BPT/active control having a 50%, 75% and 95% likelihood of being cost-effective.

Because this project uses an active control we are essentially looking at the cost-effectiveness of receiving BPT rather than other physical activities. Both BPT and the active control are delivered by a therapist and in groups. As such we are costing both interventions. However, in routine practice BPT is likely to be considered as an additional service rather than as an alternative to other active therapies. In sensitivity analyses we will therefore apply lower unit costs (25%, 50%, 75% and 100% lower) for the active control in an attempt to replicate routine practice where no or limited physical activities are provided. We will do this with caution though as it is making an implicit assumption that the active control will not be effective in reducing negative symptoms (and this may not be the case). It may of course also be the case that BPT could be more or less expensive if delivered by other professionals. As such we will increase/decrease the unit cost of BPT by 25% and 50% in sensitivity analyses.

Proposed sample size

A three point difference on the PANSS negative scale has been defined as clinically significant, which is smaller than the adjusted difference in the exploratory trial. To detect a difference of 3 points, with a standard deviation of 5, at alpha=5%, and a power of 90% 58 patients are required in each arm. Assuming an intra-cluster correlation co-efficient for 'group within therapist of 0.1, and 7 patients per therapy group with analysable data at the end of treatment gives an inflation factor of 1.6 (32) leading to a required sample size of 93 in each arm. At six months we expect a loss to follow-up of 31% resulting in 5.5 individuals per group on average and an inflation factor of 1.45; recruiting 128 per arm (16 groups of 8 in each arm) leaves 88 per arm at 6 months and 91% power to detect a difference of 3 points at this time point. Thus, we will randomise 128 patients per arm, i.e. have 16 groups of 8 in each arm. This gives increased power (94%) for our end of treatment analysis, thus allowing for a higher level of clustering than anticipated or some level of clustering at both 'group within therapist' and therapist level.

The estimated loss takes into account drop outs at three different phases of the study, i.e. a) between first interview and beginning of treatment, b) during treatment, and c) during the six months follow up period. Some patients will have to wait up to 5.5 months between giving consent and beginning of treatment. Within that period they could drop out because they change their mind about participation or experience a reduction of negative symptoms so they do not meet the inclusion criteria anymore. Based on the exploratory trial and clinical experiences in East London, we expect this drop out rate to be less than 10%. During the treatment phase we will have drop outs from treatment in both groups. In line with the intention to treat analysis we will try and follow up all patients who dropped out of treatment in either arm. However, based on our experience most patients with negative symptoms of schizophrenia who completely drop out of treatment (rather than just fail to attend a small number of sessions) also drop out of research. We expect a low drop out rate from research during treatment (7% in the exploratory trial, mainly because the control condition was

unappealing and patients then decided to drop out of treatment and subsequently also of research; also there was no reimbursement for the interview expenses/time; both issues have been addressed in the protocol for this trial). The only significant drop out rate in the exploratory trial occurred during the follow up phase.
To improve the follow up rate of 35% in the exploratory trial we will take the following steps (none of which was used in the exploratory trial):
a) patients will be reimbursed for their expenses and time for each research interview (£25 per interview);
b) at each interview (other than the final one at the end of the follow up period), research assistants will already arrange the meeting for the next interview and two weeks before the meeting send a reminder to the patient;
c) the same research assistant will conduct all four interviews with a patient so that a positive relationship can be established;
d) research assistants will work full time on the study so that they are flexible in accommodating the patients' wishes for meetings at specific times and at specific places including the patients' homes.

We therefore think that the envisaged overall follow up rate of 69% (from all patients recruited to the study) can realistically be achieved in this group of patients who are often difficult to both treat and involve in research.

Project Timetable and Milestones
The trial will be conducted over 45 months.

Month 1-3
Trial preparation with all formal approval procedures at each site and first information of services;

Month 4-6
Study preparation with the presentation of the study to services; organisation of recruitment procedures and treatment facilities at each site (for both BPT and PA); training of therapists in implementing the manual for BPT and of qualified staff to deliver the control condition.

Month 7-11
Continuing training of therapists; recruitment and baseline assessments of first groups of 16 patients per site (equivalent to 4 patients per month and site which is realistic given the experience of the exploratory trial); random allocation of patients to the two conditions.

Month 12-27
In each of three periods of 5.5 months, 16 more patients will be recruited per site and randomly allocated, resulting in a total sample of 256 patients; new therapy groups and control groups will begin about every 5.5 months (with a gap of 6 weeks between to avoid overlap); the exact length of the recruitment period for 16 new patients at each site (so that one new group each in BPT and PA can be conducted) will have some flexibility to respond to different recruitment rates over time; in case recruitment in one locality at one or more sites becomes difficult, services in a different locality at the same site will be approached and included; patients will be assessed at baseline and end of treatment; data will be continuously entered, checked and cleaned.

Month 28-31
Last group of patients will be treated and assessed before and after treatment; 6 month follow up assessments for the first two groups of recruited patients.

Month 32-37

Follow-up assessments for the latter two groups of patients, ongoing data management.

Month 28-39
Final data checking and cleaning at each site and at the co-coordinating centre.

Month 40-45
Data analysis including economic analysis, writing of report and peer-reviewed publication, further dissemination activities.

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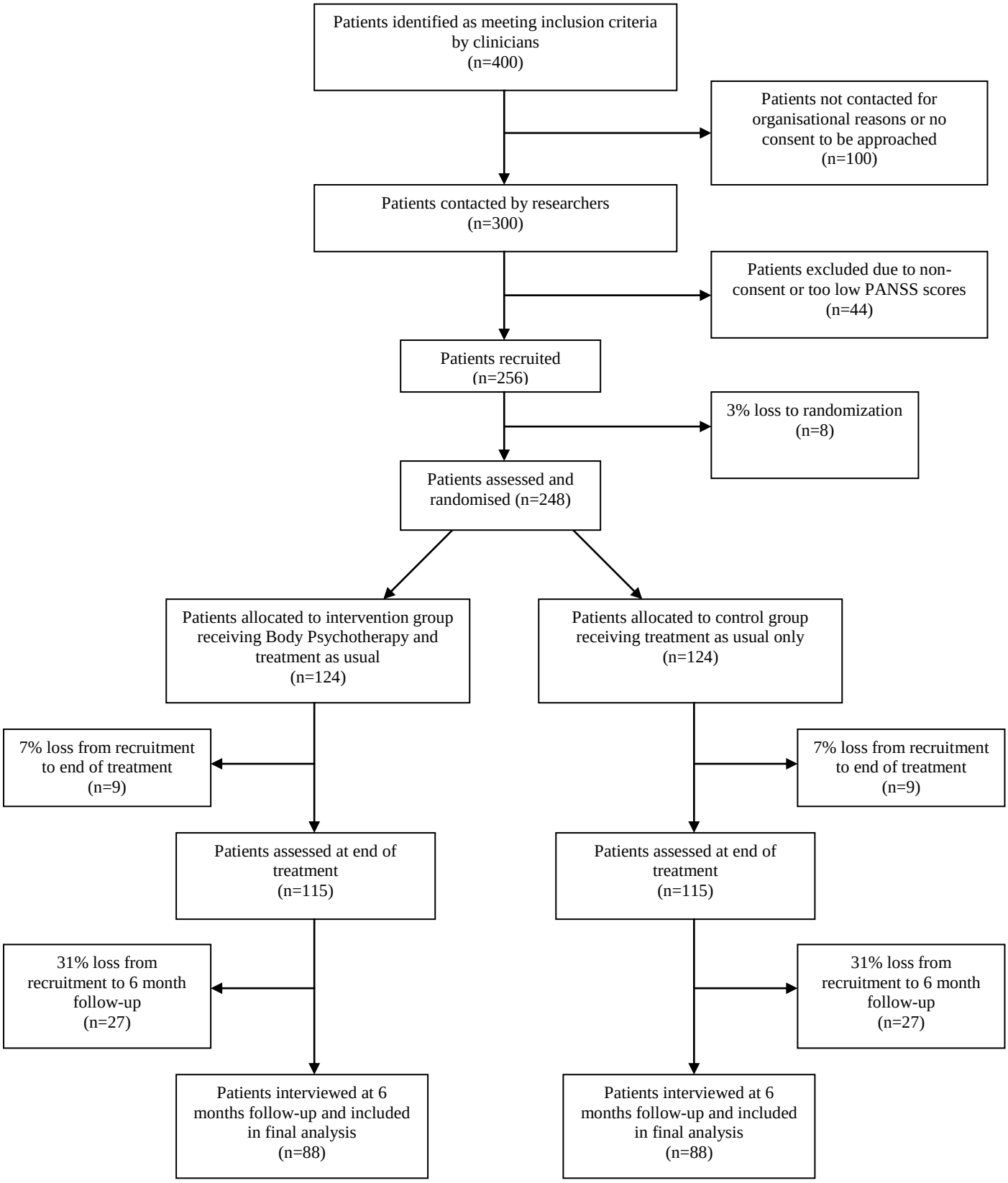
Flow Diagram



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