In Press: Journal of Personality Disorders

Psychoeducation and problem solving (PEPS) therapy for adults with personality disorder: A pragmatic randomised controlled trial to determine the clinical effectiveness and cost-effectiveness of a manualised intervention to improve social functioning

Mary McMurran, PhD[1], Florence Day, MA[2], Joseph Reilly, DM[3,4], Juan Delport, DClinPsy[5], Paul McCrone, PhD[6], Diane Whitham[2], Wei Tan, MSc[2], Conor Duggan, MD[1,7], Alan A. Montgomery, PhD[2], Hywel C. Williams, DSc,[2] Clive E. Adams, MD[1], Huajie Jin, MSc[6], Paul Moran, MD[8], and Mike J. Crawford, MD[9]

[1] Institute of Mental Health, University of Nottingham, UK

[2] Nottingham Clinical Trials Unit, University of Nottingham, UK

[3] Durham University, UK

[4] Tees, Esk & Wear Valleys NHS Foundation Trust, UK

[5] Centre for Psychological Therapies, Cwm Taf Local Health Board, UK

[6] Institute of Psychiatry, King's College London, UK

[7] Partnerships in Care

[8] Centre for Academic Mental Health, University of Bristol, UK

[9] Centre for Mental Health, Imperial College London, UK

Corresponding author: Mary McMurran, Institute of Mental Health, Triumph Road, Nottingham, NG7 2TU; mary.mcmurran@gmail.com

Abstract

We compared psychoeducation and problem solving (PEPS) therapy against usual treatment in a multi-site randomised controlled trial. The primary outcome was social functioning. We aimed to recruit 444 community-dwelling adults with personality disorder; however, safety concerns led to an early cessation of recruitment. 154 people were randomised to PEPS and 152 to usual treatment. Follow up at 72 weeks was completed for 68%. PEPS therapy was no more effective than usual treatment for improving social functioning (adjusted difference in mean Social Functioning Questionnaire scores = -0·73; 95% CI -1·83 to 0·38; P=0·19). PEPS therapy is not an effective treatment for improving social functioning of adults with personality disorder living in the community.

Introduction

Personality disorders (PD) are common long-term mental health conditions associated with a wide range of difficulties, including substance misuse, poor general health and reduced life expectancy. The management of individuals with PD is associated with substantial healthcare costs (Corulla, 2010) and the presence of co-morbid personality pathology is generally associated with a poorer treatment outcome for other health conditions. The condition is therefore associated with a high level of burden both in clinical settings as well as within the general population (Moran, 2016). Yet despite this high level of burden, knowledge about effective treatment for PD is sparse. The vast majority of treatment literature has focussed on one particular subtype – Borderline PD and we know very little about how to manage the large majority of patients meeting general criteria for PD.

Psychological treatments offer the best prospects (Bateman, Gunderson, & Mulder, 2015). However, most treatments are resource-intensive and of long duration (usually a minimum of 12-18 months). PD affects about one person in twenty (Coid, Yang, Tyrer, Roberts, & Ullrich, 2006), which limits the amount of services that can be provided so that the great majority of people who may benefit from psychological treatments do not receive them. Testing the effectiveness and cost-effectiveness of shorter interventions is therefore important if more people with PD are to be treated effectively. Additionally, interventions that can be used with any PD have the potential to alleviate the burden on clinical services that can be created if specific types of PD need to be identified for treatment allocation, particularly when diagnostic co-occurrence is the rule rather than the exception. In treating groups of people with mixed PDs, the treatment target necessarily needs to be a problem common to all.

One core defining feature of all PDs is the experience of problems with social and interpersonal functioning (Nur, Tyrer, Merson, & Johnson, 2004). This points to the potential value of social problem solving therapy, the aim of which is to help people recognise their strengths and limitations and to learn new skills that will enable them to cope more effectively with life's problems. PD is associated with problem-solving deficits (Bray, Barrowclough, & Lobban, 2007; Dixon-Gordon, Chapman, Lovasz, & Walters, 2011; Herrick & Elliot, 2001; McMurran, Oaksford, & Christopher, 2010) and meta-analyses have demonstrated the value of problem-solving therapy in the treatment of a range of mental

health problems (Bell & D'Zurilla, 2009; Cuijpers, van Straten, & Warmerdam, 2007; Kirkham, Choi, & Seitz, 2016; Malouff, Thorsteinsson, & Schutte, 2007). Psychoeducation about PD aims to educate, build rapport, and motivate people for problem solving therapy. Psychoeducation has been shown to improve the therapeutic alliance (Banerjee, Duggan, Huband, & Watson, 2006), and reduce impulsivity and improve close relationships with people with borderline PD (Zanarini & Frankenburg, 2008).

In light of the existence of these two promising candidate treatments, a combined psychoeducation and problem solving (PEPS) therapy was designed and evaluated with community adults with PD in an exploratory randomised trial (Huband, McMurran, Evans, & Duggan, 2007). The study suggested that compared to a wait-list control group, PEPS therapy improved social functioning, as measured by the Social Functioning Questionnaire (Tyrer et al., 2005). The aim of this study was to compare the clinical and cost-effectiveness of PEPS therapy in addition to usual treatment with usual treatment alone in an adequately powered, multisite RCT.

Methods

Design

The PEPS trial was a two-arm, parallel group, pragmatic randomised controlled superiority trial.

Participants

Participants were recruited from mental health services in three UK NHS trusts. At the point of randomisation, participants were required to have one or more PD (including PD Not Otherwise Specified; PD NOS), identified through the International Personality Disorder Examination (IPDE) (Loranger, 1999). Participants were aged 18 or over, living in the community, proficient in spoken English and had capacity to provide informed consent. Exclusion criteria were a primary diagnosis of major functional psychosis, insufficient degree of literacy, comprehension or attention to be able to engage in trial therapy and assessments, engagement in a specific programme of psychological treatment for personality disorder or likely to start such treatment during the trial period, and participation in any other trial. Participants reaching the final follow-up were offered a non-contingent voucher payment of £20 in recognition of their contribution to the trial.

Randomisation and blinding

Following baseline assessments, participants were randomly allocated to receive PEPS therapy in addition to usual treatment or usual treatment only at a ratio of 1:1. Randomisation was based on a computer generated pseudo-random code using random permuted blocks of randomly varying size created by the Nottingham Clinical Trials Unit (NCTU) in accordance with their standard operating procedure and held on a secure server. The randomisation was stratified by recruiting centre and sex. The sequence of treatment allocations was concealed until recruitment, data collection, and all other trial-related assessments were complete. The investigator, or an authorised designee, accessed the treatment allocation for each participant by means of a remote, internet-based randomisation system developed and maintained by the NCTU. Allocation was therefore fully concealed from recruiting staff.

Participants, mental health workers delivering the interventions, and participants' usual care teams were aware of the treatment allocation. The primary outcome, mental health, service use, and quality of life data were obtained from self-report questionnaires from participants who were not blind to treatment allocation. However, outcome measures were administered by research assistants blind to treatment allocation in order to reduce assessment bias and data entry from these questionnaires, and all data analyses were conducted blind to allocation. A record was made of the blinding status of the researcher conducting the final follow-up data collection.

Interventions

Psychoeducation with problem solving (PEPS) therapy is a complex cognitive-behavioural intervention with two distinct components. Psychoeducation consists of up to four individual sessions in which participants are asked about their understanding of personality and any personality-related problems that they experience, followed by information on their personality disorder diagnoses as identified at screening using the IPDE Participants are then asked to identify specific problems that they want to change, and prioritise those to be addressed in the subsequent treatment sessions. Problem solving therapy is a 12 x 2-hour session, manualised, group intervention designed to improve interpersonal problem solving skills. In each session, one participant works through a problem that has been identified in collaboration with a group facilitator. This process involves identifying negative feelings and using these as a cue for initiating the problem solving process; defining problems clearly and

accurately; setting specific goals for change; generating solution options; considering the consequences of each option to self and others; and selecting potentially effective options and organising these into an action plan. Participants are offered optional fortnightly individual support sessions throughout the 12-week problem solving therapy group to help implement their action plans. Throughout this process, attention is paid to improving optimism and hope for change, which is regarded as of equal importance to the development of problem solving skills.

Usual treatment was provided by participants' care teams in accordance with recommended clinical practice. According to National Institute for Health and Clinical Excellence (NICE) Guidelines this should include assessment, care planning, risk assessment, and psychological interventions.

Treatment fidelity

Treatment fidelity was promoted in a number of ways: the IPDE, psychoeducation, and problem solving therapy were comprehensively manualised; therapists were qualified mental health nurses or psychology graduates with clinical experience; staff were trained and supervised in the IPDE, psychoeducation, and problem solving therapy; an audiotape of delivery for each therapist was scrutinised by the trainers to ensure that each therapist was adhering to the treatment specification according to competence checklists constructed for the IPDE and problem solving sessions; adherence to psycho-education was self-rated by the therapist after the end of all psycho-education sessions, using a standard protocol. Additionally, treatment fidelity was assessed by measuring adherence to protocol implementation (e.g. frequency and duration of treatment sessions).

Follow-up

Follow-up visits were completed in person, or by telephone. To improve response rates at the final follow-up, the SFQ was posted to participants who could not be contacted by another means. Assessments were self-completed by participants or read aloud to participants by the researcher if required. No test feedback was given to participants.

Outcome measures

Replicating the pilot study (Huband et al., 2007), the primary outcome was social functioning measured by the Social Functioning Questionnaire (SFQ) at 72-week follow-up. The SFQ is

an 8-item self-report scale, with items covering 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 on a scale from 0 to 3. SFQ scores correlate well with measures of psychiatric distress and are stable over time. A reduction (i.e., an improvement) of 2 points or more on the SFQ was the specified clinically significant change, based on evidence from an RCT of cognitive behaviour therapy in health anxiety that a reduction of 2 points or more was associated with reductions in anxiety, depression, and service use (Seivewright et al., 2008). Secondary outcomes were: scheduled and unscheduled health service use collected through a retrospective review of mental health service and GP records; mood, measured by the Hospital Anxiety and Depression Scale (HADS; Zigmond & Snaith, 1983) and the client's assessment of severity on a scale from not at all distressing (0) to very distressing (10) of the three problems they considered most important (Three Main Problems). Health economic outcomes were assessed by the Client Service Receipt Inventory (CSRI; Beecham & Knapp, 2001) and the European Quality of Life scale (EQ-5D; EuroQoL Group, 1990). In addition, the Social Problem Solving Inventory – Revised (SPSI-R; D'Zurilla, Nezu, & Maydeu Olivares, 2002) was measured after the problem solving intervention or at an equivalent time to examine the process of change. A service use record check was completed after the final assessment measures had been collected. Data were collected from GP and mental health records retrospectively for the duration of the trial.

Adverse events

Adverse events were defined as death for any reason, inpatient hospitalisation for any reason, and any other serious, unexpected adverse event. Adverse events were recorded for all participants from consent to trial completion or early withdrawal from trial follow-up.

Sample size

The trial was designed to detect a between-group difference of two points on the SFQ score, regarded as a clinically important effect (Seivewright et al., 2008). With estimated maximum standard deviation (SD) of $4{\cdot}5$[16], 80% power and two-sided 1% alpha, 120 participants in each arm are required for analysis. In anticipation of a 30% loss to follow-up at 72 weeks after randomisation, we planned to randomise 340 participants (170 in each arm).

Statistical analyses

The primary analysis (intention-to-treat; ITT) compared mean SFQ score between PEPS and usual treatment at 72 weeks post-randomisation follow up, adjusted for baseline SFQ score and stratification variables (centre and gender), and implemented using multivariable linear regression. Participants were analysed as randomised, and all were included in the primary analysis by imputation of missing data. The imputation model included site, age, gender, ethnicity, socioeconomic status, PD category (i.e., simple or complex PD), SFQ at baseline and 24 weeks, baseline EQ-5D, baseline HADS, baseline SPSI-R, and baseline Three Main Problems, and 20 datasets were imputed. We obtained robust variance estimates in all regression models to allow for the potential clustering effect of receiving therapy in groups in the PEPS arm.

We conducted the following sensitivity analyses of the primary outcome. We repeated the primary analysis with additional adjustment for any variables displaying marked imbalance between the arms at baseline. We repeated the primary analysis restricted to those participants with observed primary outcome data at 72 weeks. To examine treatment efficacy, Complier-Average Causal Effect (CACE) estimates (Dunn, Maracy, & Tomenson, 2005) for participants in the PEPS arm defined as having received the intervention in line with the treatment protocol were estimated using instrumental variable regression. The definition of treatment received as per protocol was having completed psychoeducation according to the therapist assessment and attended a minimum of six of the group problem-solving sessions.

We conducted pre-specified sub-group analyses of the primary outcome according to study site, whether the participant had simple or complex personality disorder, and whether the participant did or did not have borderline personality disorder at baseline. Personality disorder is considered simple when criteria are met for one or more DSM cluster of problems; people with complex PD have disorders in more than one cluster (Tyrer & Johnson, 1996).

Analysis of secondary outcomes was conducted using a similar approach as for the primary outcome, except that missing data were not imputed, and choice of regression model and presentation of the estimated between-group effect was dependent on outcome type.

Economic evaluation

The objectives of the economic evaluation were to measure and describe healthcare and societal costs of participants in the PEPS trial in the 6 months prior to randomisation and to compare patterns and costs of service utilisation at the final follow-up (week 72) across usual treatment and PEPS. The costs of each resource item were calculated using best available unit cost estimates and reported in 2012/13 prices (Curtis, 2013). The cost of the PEPS intervention was estimated using information on the core resources required to deliver the individual and group sessions, and estimating specific costs for those inputs. Costs were calculated using data on the number of therapy sessions received by each participant. Bootstrapped estimates were planned so that mean costs could still be compared whilst imposing no prior assumptions regarding the data distribution. Baseline data were analysed using a regression model to identify variables significantly associated with cost.

Research governance

The study was conducted in accordance with the principles of Good Clinical Practice and the Research Governance Framework for Health and Social Care and registered prior to recruitment of first participant with Current Controlled Trials as ISRCTN70660936. Ethical approval for the study, including amendments, was given by the South Wales Research Ethics Committee (Ref. 09/WSE03/48). Robust trial governance was in place and consisted of a Trial Management Group (TMG); an independent Trial Steering Committee (TSC) and a Data Monitoring and Ethics Committee (DMEC) that provided independent oversight of the trial including safety and efficacy indications.

Safety monitoring

Adverse events were identified by asking participants for information during each contact, asking the participant's clinical team to inform the site Principal Investigator if an adverse event was identified, and contacting the participant's responsible clinician by letter to request information. In the event of loss to follow-up, the participant's clinical team and / or GP was contacted to request information on any unreported adverse events. All adverse events were routinely reported to the Research Ethics Committee, TSC and DMEC. Serious adverse events that were thought to be related to the trial procedures and that were not identified as expected occurrences were reported immediately to the research ethics committee, as required by the National Research Ethics Service (NRES) guidance.

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Between August 2010 and November 2012, 739 people were referred to the trial for assessment of eligibility, of whom 444 (60% of those referred) were initially assessed as eligible and provided consent to participate in the trial, and 306 (69% of those eligible) were randomised (Figure 1). Two months before the end of the 32-month recruitment phase of the study the DMEC issued a safety alert, following review of unblinded data. The TSC advised that no further patients should be randomised into the PEPS trial, patients currently in treatment should no longer receive the trial treatment, and the investigators should inform patients of the possibility of harm. Their advice was that all patients should be followed up as per trial protocol. When the decision to stop recruitment and delivery of the trial therapy was made, 306 participants had been randomised (90% of the target of 340).

Follow up was greater in the PEPS arm at every time point. At the primary follow up 72 weeks after randomisation, data were collected from 62% and 73% in the usual treatment and PEPS arms respectively. Total person-years of follow up were 178 and 203 in the usual treatment and PEPS arms respectively.

Table 1 summarises the baseline characteristics of the groups. The only variable with a notable imbalance between the arms at baseline was type of personality disorder, with a greater proportion in the PEPS arm defined as complex (60% compared with 49% in usual treatment).

Of those randomized to the PEPS arm, 4% (n=6) received no intervention at all, 51% (n=78) received a partial intervention (i.e., 5 or fewer group sessions), and 45% (n=70) received the intervention as per protocol (i.e., 6 or more group sessions).

The primary ITT analysis found no evidence of any clinically important difference between the arms in mean SFQ at 72 weeks (Table 2). There were no statistically significant

differences in either of the secondary outcomes – mood, measured by the HADS and self-rated problem severity – or the proposed mechanism of change - problem solving as measured by the SPSI-R (see Table 2). Although the effect of PEPS was somewhat increased when accounting for treatment compliance and when restricted to participants with observed follow up data, there was no strong evidence of a between-group difference in the primary outcome from the sensitivity analyses (Table 3). There was no evidence that PEPS was differentially effective according to study site (P=0·3) or PD simple/complex category (P=0·93) or having / not having borderline PD at baseline (P=0.39) (data not shown).

Service use data are presented in Table 4 for 126 (83%) and 140 (91%) participants in usual treatment and PEPS arms respectively. There were 2064 contacts with health services from 116 individuals allocated to usual treatment compared with 2041 from 135 individuals in the PEPS arm. There was no evidence of any differences between groups in total health service use or for service use classified as scheduled and unscheduled.

A total of 76 adverse events from 39 individuals and 117 adverse events from 60 individuals were reported in the usual treatment and PEPS arms respectively (see Table 5). There were four deaths reported during the study, two due to natural causes and two due to suicide. All four participants were allocated to the PEPS arm. The nature and circumstances of these deaths did not seem related to the therapy. There was an excess of participants in the PEPS arm who reported at least one adverse event compared with usual treatment, which was attenuated after allowance for the difference in total follow up between the arms (Table 6).

Economic analysis

The total cost of all healthcare services at baseline was £265 higher in the usual treatment group compared to the PEPS group: means for 6 months prior to baseline were £4178 (SD=£5,780) for usual treatment and £3,913 (SD=£5,834) for PEPS. For baseline to the final follow-up, the mean costs for the usual treatment group were £8072 (£10,598) and for the PEPS group were £6,777 (SD=£10,550). After adjusting for differences in baseline costs, there was a non-significant difference in favour of PEPS (-£1,174, 95%CI -£3,720, £1,371, P=0.19). When the cost of the PEPS intervention was considered, the total costs for the PEPS group increased to £7,727 per patient for the entire follow-up period, which is still lower than the total cost of usual treatment group (£8,072 per patient).

The mean utility values derived from the EQ-5D at the final follow-up were not significantly different between the usual treatment (M=0·38, SD=0·37) and PEPS groups (M=0·39, SD=0·37) (P=0·88). The mean QALY gain between baseline and final follow-up was 0·57 for the usual treatment group and 0·56 for the PEPS group. The adjusted difference was 0·02 (95%CI -0·06, 0·09) in favour of PEPS. In a technical sense, PEPS was seen to be dominant as it resulted in lower total costs and a greater QALY gain after adjusting for baseline. However, this does not take uncertainty around these estimates into account. Based on the cost-effectiveness acceptability curve (CEAC) for the whole follow-up period, there is a likelihood of 58% that PEPS is the more cost-effective option. Whilst we do not know the true societal value that should be placed on a QALY gain, NICE uses a threshold in the region of £20,000-£30,000. Between these two levels there is a 63·6% to 64·2% likelihood that PEPS is the more cost-effective option.

Discussion

Summary of findings

PEPS therapy plus usual treatment was no more effective than usual treatment alone in terms of improving global social functioning of participants in this trial. The confidence interval for the between-group difference in mean SFQ from the primary analysis excluded the pre-specified minimum important difference of two points. There were no treatment effects evident for any of the secondary outcomes. Subgroup analysis of the SFQ at 72-week follow-up showed no difference in outcome either by study site or for complex versus simple personality disorder. About half of the people in the PEPS arm did not receive the full dose of treatment. Analysis of the primary outcome by compliance suggested a better outcome for those who received an adequate amount of treatment. PEPS shows slightly lower costs and higher Quality Adjusted Life Years (QALYs), but differences are not large or significant and confidence intervals are wide. There is a 64% likelihood that the intervention is cost-effective at the threshold used by NICE.

The DMEC, after studying unblinded data, alerted the TSC to the higher rate of adverse events in the PEPS arm of the trial. The TSC advised that recruitment to the trial be stopped, that treatment should discontinue, and that all participants should be alerted to this safety signal. The TSC also firmly advised that follow-up should continue. By the end of the trial, both the number of adverse events, including serious adverse events, and the number of

people reporting them were greater in the PEPS arm, although there was no strong statistical evidence of a difference between arms.

Strengths and Limitations

This was a pragmatic trial with broad inclusion criteria (i.e., any personality disorder). As such, it presents results that are generalizable to regular clinical practice in secondary care mental health services. A number of strategies were in place to maximise treatment fidelity, which is the extent to which the intervention was delivered as specified in the protocol. Hence, the observed outcomes are unlikely to be the result of failure to implement the model as intended. Validated outcome and process measures were used in this trial. One limitation is that the primary outcome was assessed via a brief self-report measure; however, this was augmented by objective secondary outcomes such as service usage. With regard to secondary outcomes of service usage, the original idea was that service use might not decline as a result of treatment but that better use of the services offered might result. That is, treated individuals might attend scheduled appointments and thereby avoid crises that required emergency, unscheduled appointments. In the event, it was not easy to ascertain which appointments were scheduled and which were not, apart from the most obvious ones such as Emergency Department visits.

The study fell short of its target of 70% follow-up, with an overall follow-up at the 72-week endpoint being 68%. Participants in the PEPS arm were more likely to be followed up at 72 weeks, and remain in the trial for longer among those who were not followed up at 72 weeks. Compared with the primary analysis, the point estimates for sensitivity analyses based on observed data were larger and 95% confidence limits included the pre-specified clinically important difference of two points. However these are likely to be subject to bias, and while analyses involving multiple imputation of missing outcome data also require some assumptions, we do not consider there to be a high probability of having failed to identify a clinically important treatment effect.

Care was taken to minimise bias through independent randomisation, masking researchers collecting follow-up data, and conducting data entry, cleaning and analysis while blind to intervention status. In contrast, recording of adverse event recording was highly likely to be subject to bias. Participants in the PEPS arm had greater contact with staff, allowing more opportunity to report adverse events and they may also have felt able to be more candid about

adverse events. A greater degree of contact with participants in the PEPS arm may have led to the identification of more problems by staff. Also, clinicians may have been more likely to advise the research therapists about adverse events for those in PEPS therapy and to manage the usual treatment participants themselves. Alternatively, PEPS may encourage help seeking, increasing the likelihood of hospitalisation, in which case adverse events would not be literally 'adverse'. More systematic and objective recording of adverse events would have been desirable.

About half of those randomised to the PEPS arm received only a partial intervention (i.e., five or fewer group sessions) and the planned 12-session group intervention actually lasted on average six sessions. Complier-Average Causal Effect (CACE) analysis suggests a possible greater effect of PEPS among compliers, but the sensitivity analyses do not offer any strong support for the effectiveness of the intervention. Of the psychoeducation sessions offered (on average 3·4), 90% were taken up. Clearly, individual psychoeducation is far better attended than subsequent group sessions, and the overall group non-completion rate is high. This difference may be explained in a number of ways. Participants' enthusiasm for treatment may be stronger at the start of treatment and wane with time, they may prefer individual sessions, or the content of psychoeducation may be more relevant to their problems.

The content of usual treatment was not standardized in this trial. Imposing standard treatment on the large number of services contributing to this trial was not considered a feasible option. Practice varied widely across services, and usual treatment was not a clearly prescribed procedure. Some participants commented that usual treatment could be well planned, holistic, and reliably delivered, but in other cases it was unfocused and unreliable.

Interpretation

This full-scale trial of PEPS therapy indicates that treatment did not improve social functioning or mental wellbeing and did not reduce service use. These findings are in contrast to those derived from the pilot study. Yet, it is not unusual that positive findings emerging from small exploratory trials are not replicated when tested in a large pragmatic design. The full trial was superior in its design and methods: it was multisite, there was a larger number of participants, providing greater precision of estimated between-group differences, the follow-up period was considerably longer, and the methods of imputing missing data were more sophisticated. Hence, greater confidence can be placed in these results.

Most of the treatments for personality disorder that are evidenced as effective are of relatively long duration and are delivered by highly-trained personnel, and hence are costly to deliver and are consequently of restricted availability. Current NICE guidelines recommend that brief interventions of less than three months duration should not be offered to those with borderline personality disorder. The question of whether brief interventions work for PD was recently investigated with insufficient available evidence to provide an answer (Omar, Tejerina-Arreal, & Crawford, 2014). However the null findings of the PEPS trial and the possibility of increased help seeking among those offered PEPS therapy supports the conclusions of NICE that, outside of research studies, brief interventions should not be offered to people with personality disorder.

Recently, evidence has been accruing from trials that structured clinical management achieves equally good outcomes as specific treatments for personality disorder (Bateman & Fonagy, 2009). Service users and providers have also highlighted the importance of coordinating and integrating psychological treatments within teams that can provide additional support for patients at times of crisis (Crawford et al., 2008). In the PEPS trial treatment was delivered as a standalone therapy rather than being integrated into a coordinated package of care. One explanation for a higher number of reported events in the treatment arm of the PEPS trial is that the treatment stopped without any structured follow-up, thus leaving participants unsupported after a period of treatment. Trialists working in this field should be vigilant for AEs, including the potential impact of help seeking (via hospitalisation) as an AE, and should record AEs equitably across arms (Duggan, Parry, McMurran, Davidson, & Dennis, 2014).

Conclusions

This rigorous trial has established that PEPS therapy is not an effective treatment for improving social functioning and mental health in community adults with PD. This is despite PEPS being based on solid theoretical and empirical foundations, on therapy components with demonstrated effectiveness in dealing with a range of psychological problems, and which those who have received it have deemed helpful. This is not the first psychosocial intervention that has appeared promising - theoretically, empirically, and by favourable participant judgement – but has proved in rigorous trials to be ineffective, or even harmful.

Information from this study indicates that people with personality disorder have poor quality of life and are heavy users of health and social services. It is important to continue to seek effective management and treatment for this group of troubled individuals. Good quality research is the only way to provide evidence of what is genuinely effective – or ineffective – and is the best way to serve patients, their family and friends, and our wider society. Such research is expensive, but the costs of not conducting such research may well be greater.

Contributors

MM was the chief investigator. FD was trial manager. MM, HW, MC, FD, DW, PMcC, CD, CA, and PM contributed to the study concept and design. JR, JD, and MC were site co-investigators. AM and WT developed the statistical analysis plan and conducted the analyses. PMcC and HJ designed the economics analysis plan and conducted the economics analysis. MM interpreted the data and wrote the report in collaboration with all authors.

Declaration of interests

All authors have completed the unified competing interest form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare (1) no financial support for the submitted work from anyone other than their employer; (2) no financial relationships with commercial entities that might have an interest in the submitted work; (3) no spouses, partners, or children with relationships with commercial entities that might have an interest in the submitted work; and (4) no non-financial interests that may be relevant to the submitted work.

Hywel Williams is Director of the NIHR Health Technology Assessment Programme.

Acknowledgements

This research was supported by funding from the National Institute for Health Research Health Technology Assessment Programme (Ref: 08/53/06).

We thank all those who took part in the trial and clinical staff at the participating sites for their support.

We acknowledge the support of the National Institute for Health Research, through the Mental Health and Primary Care Research Networks, and the National Institute for Social Care and Health Research (NISCHR) in Wales.

The full report is published in the online journal, *Health Technology Assessment* (http://www.journalslibrary.nihr.ac.uk/hta/volume-20/issue-52#abstract).

References

Banerjee, P., Duggan, C., Huband, N., & Watson, N. (2006). Brief psychoeducation for people with personality disorder: a pilot study. *Psychology & Psychotherapy: Theory, Research & Practice*, *79*, 385–394.

Bateman, A., & Fonagy, P. (2009). Randomized controlled trial of outpatient mentalization-based treatment versus structured clinical management for borderline personality disorder. *American Journal of Psychiatry*, *166*, 1355–1364.

Bateman, A.W., Gunderson, J., & Mulder, R. (2015). Treatment of personality disorder. *The Lancet, 385*, 735–743.

Beecham, J., & Knapp, M. (2001). Costing psychiatric interventions. In G. Thornicroft (ed). Pp. 200–224. *Measuring mental health needs*. London, UK: Gaskell.

Bell, A.C., & D'Zurilla, T.J. (2009). Problem-solving therapy for depression: A meta-analysis. *Clinical Psychology Review*, *29*, 348–353.

Bray, S., Barrowclough, C., & Lobban, F. (2007). The social problem-solving abilities of people with borderline personality disorder. *Behaviour Research & Therapy*, *45*, 1409–1417.

Coid, J., Yang, M., Tyrer, P., Roberts, A., & Ullrich, S. (2006). Prevalence and correlates of personality disorder in Great Britain. *British Journal of Psychiatry, 188*, 423–431.

Corulla, W.J. (2010). Personality disorder: Incidence, co-morbid disorders, and cost within a northern mental health trust. *Personality & Mental Health*, *4*, 206–214.

Crawford, M.J., Price, K., Rutter, D. et al. (2008). Dedicated community-based services for adults with personality disorder: A Delphi study. *British Journal of Psychiatry, 193*, 342–343.

Cuijpers, P., van Straten, A., & Warmerdam, L. (2007). Problem solving therapies for depression: A meta-analysis. *European Psychiatry*, *22*, 9–15.

Curtis, L. (2013). *Unit costs of health and social care 2013*. Canterbury, UK: Personal Social Services Research Unit.

Dixon-Gordon, K.L., Chapman, A.L., Lovasz, N., & Walters, K. (2011). Too upset to think: the interplay of borderline personality features, negative emotions, and social problem solving in the laboratory. *Personality Disorders: Theory, Research & Treatment, 2*, 243–260.

Duggan, C., Parry, G., McMurran, M., Davidson, K., & Dennis, J. (2014). The recording of adverse events from psychological treatments in clinical trials: Evidence from a review of NIHR-funded trials. *Trials, 15*, 335.

Dunn, G., Maracy, M., & Tomenson, B. (2005). Estimating treatment effects from randomised clinical trials with noncompliance and loss to follow-up: The role of instrumental variable methods. *Statistical Methods in Medical Research, 14*, 369–395.

D'Zurilla, T.J., Nezu, A.M., Maydeu Olivares, A. (2002). *Social Problem-Solving Inventory–Revised (SPSI-R): Technical manua*l. North Tonawanda, NY: Multi-Health Systems, Inc.

EuroQol Group. (1990). EuroQol: A new facility for the measurement of health-related quality of life. *Health Policy, 16,* 199–208.

Herrick, S.M., & Elliott, T.R. (2001). Social problem-solving abilities and personality disorder characteristics among dual-diagnosed persons in substance abuse treatment. *Journal of Clinical Psychology, 57,* 75–92.

Huband, N., McMurran, M., Evans, C., & Duggan, C. (2007). Social problem-solving plus psychoeducation for adults with personality disorder: Pragmatic randomised controlled trial. *British Journal of Psychiatry, 190,* 307–313.

Kirkham, J.G., Choi, N., & Seitz, D.P. (2016). Meta-analysis of problem solving thereapy for the treatment of major depressive disorder in older adults. *International Journal of Geriatric Psychiatry, 31,* 526–535.

Loranger, A.W. (1999). *International Personality Disorder Examination (IPDE*). Odessa, Florida: Psychological Assessment Resources Inc..

Malouff, J.M., Thorsteinsson, E.B., & Schutte, N.S. (2007). The efficacy of problem solving therapy in reducing mental and physical health problems: A meta-analysis. *Clinical Psychology Review, 27,* 46–57.

McMurran, M., Oaksford, M., & Christopher, G. (2010). Does social problem solving mediate the relationship between personality traits and personality disorders? An exploratory study with a sample of male prisoners. *Personality & Mental Health, 4,* 180–192.

Moran, P**.** (2016). The influence of personality disorder on the future mental health and social adjustment of young adults: a population-based cohort study. *The Lancet,* in press.

Nur, U., Tyrer, P., Merson, S., & Johnson, T. (2004). Relationship between clinical symptoms, personality disturbance, and social function: A statistical enquiry. *Irish Journal of Psychological Medicine, 21,* 19–22.

Omar, H., Tejerina-Arreal, M., & Crawford, M.J. (2014). Are recommendations for psychological treatment of borderline personality disorder in current UK guidelines justified? Systematic review and subgroup analysis. *Personality & Mental Health, 8,* 228–237.

Seivewright, H., Green, J., Salkovskis, P., Barrett, B., Nur, U., & Tyrer, P. (2008). Cognitive-behavioural therapy for health anxiety in a genitourinary medicine clinic: Randomised controlled trial. *British Journal of Psychiatry, 193,* 332–337.

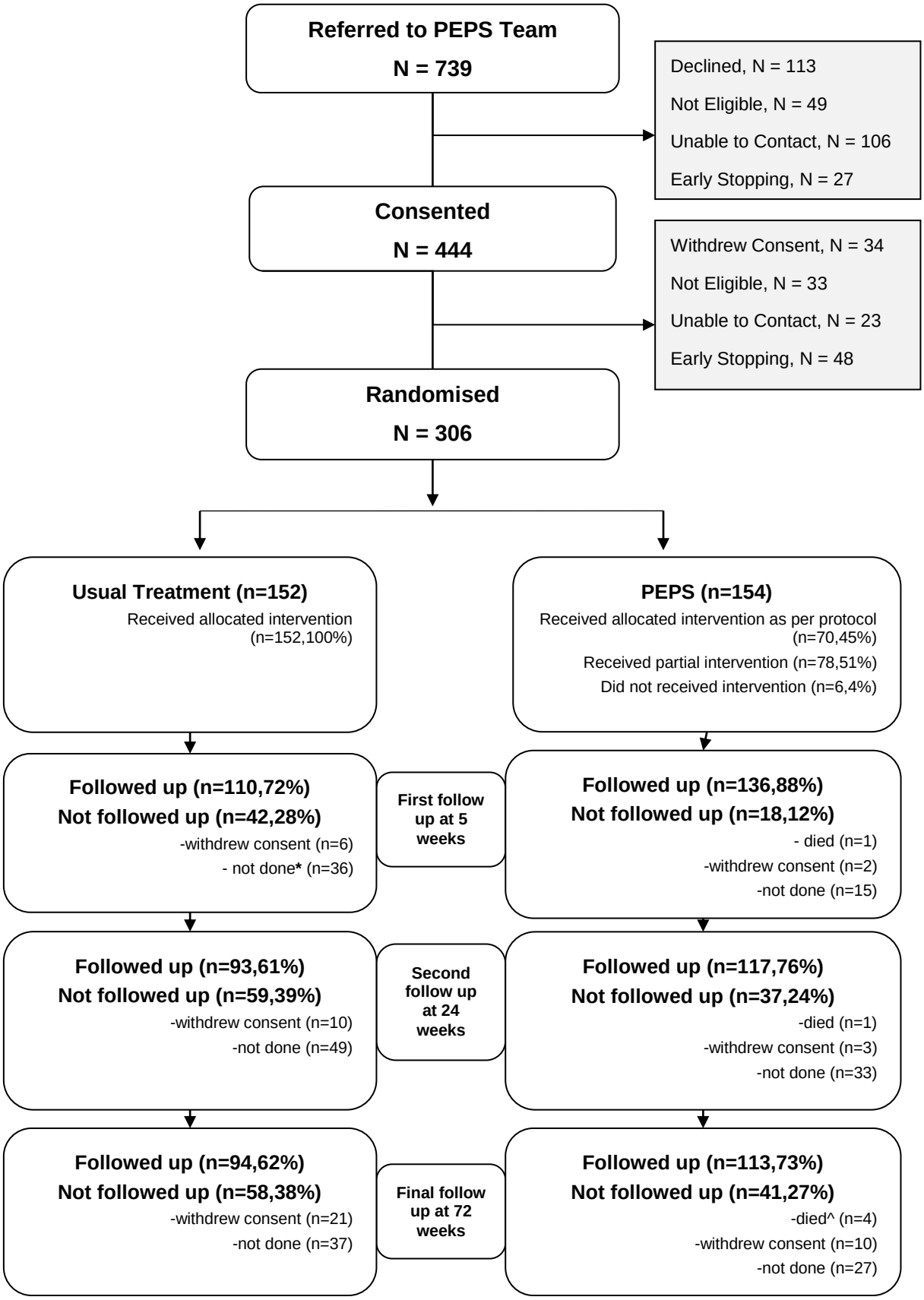
Tyrer, P., & Johnson, T. (1996). Establishing the severity of personality disorder. *American Journal of Psychiatry, 153,* 1593–1597.

Tyrer, P., Nur, U., Crawford, M., et al. (2005). The Social Functioning Questionnaire: A rapid and robust measure of perceived functioning. *International Journal of Social Psychiatry*, *51*, 265–275.

Zanarini, M.C., & Frankenburg, F.R. (2008). A preliminary, randomized trial of psychoeducation for women with borderline personality disorder. *Journal of Personality Disorders*, *22*, 284–290.

Zigmond, A.S., & Snaith, R.P. (1983). The hospital anxiety and depression scale. *Acta Psychiatrica Scandinavica*, *67*, 361–370.

Figure 1. Consort Diagram



*not done is a combination of those who did respond to contact and those who chose not to attend follow up for that particular follow up.

^two of the deaths happened before and two happened after the trial being stopped.

Table 1: Summary of participant characteristics at baseline by trial arm

Variable	Treatment arm	
	Usual Treatment (n=152)	**PEPS (n=154)**
Age at randomisation (years)		
Mean[SD]	37·8[11·0]	38·6[10·9]
Gender		
Female	115(76)	115(75)
Male	37(24)	39(25)
Age left full time education (years)		
Mean[SD]	16·9[3·3]	17·2[3·7]
Highest educational attainment		
None	29(19)	24(16)
GCSE	16(10)	22(14)
A-level	45(30)	35(23)
Vocational	10(7)	10(7)
Degree	32(21)	36(23)
Other	20(13)	25(16)
Missing	0	2(1)
Ethnicity		
White	127(83)	129(84)
Mixed	9(6)	6(4)
Black-Caribbean	6(4)	5(3)
Black-African	0	2(1)
Black-other	2(1)	0
Asian-Indian	1(2)	0
Asian-other	1(1)	0
Other	6(4)	12(8)
Socio-economic status		
Never worked and long term unemployed	96(63)	105(68)
Routine and manual occupations	28(18)	20(13)
Intermediate occupations	13(9)	9(6)
Managerial and professional occupations	15(10)	20(13)
IPDE type (definitive)[a]		
Paranoid	16(11)	13(8)
Schizoid	1(1)	4(3)
Schizotypal	0	0
Antisocial	31(20)	23(15)
Borderline	90(59)	93(60)
Histrionic	6(4)	2(1)
Narcissistic	3(2)	1(1)
Avoidant	56(37)	57(37)
Dependent	7(5)	4(3)
Obsessive-compulsive	20(13)	14(9)
PD not otherwise specified	10(7)	14(9)
Personality Disorder (PD)		
Simple PD	77(51)	61(40)
Complex PD	75(49)	93(60)

All data are N (%) unless specified; [a] Participants may have more than one type

Table 2. Primary and secondary outcomes at 72-week follow-up

	Treatment arm		**Adjusted[b] difference in means**	**95% CI**	**P value**
	Usual Treatment (n=152)	**PEPS (n=154)**			
Social Functioning Questionnaire					
Mean at baseline [SD]	14·3[4.5]	15·0[4·0]			
Mean at 72 weeks[a] [SD]	13·8[5·0]	13.5[5.0]	-0·73	-1·83, 0·38	0·19
Hospital Anxiety and Depression Scale					
Mean at baseline [SD]	27·5[7·5]	27·4[7·2]			
Mean at 72 weeks [SD]	22·3[11·8]	21·0[10·9]	-1·2	-4·2,1·8	0·44
Three Main Problems					
Mean at baseline [SD]	8·7[1·1]	8·7[1·1]			
Mean at 72 weeks [SD]	6·6[2·8]	6·3[2·8]	-0·3	-1·0,0·5	0·48
Social Problem Solving Inventory - Revised					
Mean at baseline [SD]	6.9[3·3]	6·4[3·0]			
Mean at 72 weeks [SD]	8·2[4·0]	8·0[4·0]	0·14	-0·5,0·8	0·68

[a] Based on imputed data

[b] Adjusted by baseline score, study centre, gender.

Table 3: Sensitivity analysis of primary outcome

	Analysis type	Adjusted difference in means	95% CI	P value
1	Primary analysis (MI[a])	-0·73	-1·83,0·38	0·19
2	As (1) with adjustment for baseline PD type	-0·72	-1·78,0·34	0·18
3	As (1), CACE[b] estimate	-1·60	-3·96,0·76	0·18
4	Observed outcome data	-1·07	-2·24,0·09	0·07
5	As (4), CACE estimate	-2·15	-4·39,0·09	0·06

[a] Multiple Imputation of missing data

[b] Complier-Average Causal Effect

Table 4: Use of health services

	Treatment arm		Incidence Rate Ratio[a]	95% CI	P value
	Usual Treatment (n=140)	PEPS (n=126)			
Annual rate of scheduled service use Mean at 72 weeks [SD]	6·5[7·4]	6·0[5·5]	0·91	0·69, 1·21	0·54
Annual rate of unscheduled service use Mean at 72 weeks [SD]	4·4[6·2]	3·7[4·3]	0·87	0·60, 1·26	0·47
Annual rate of service use overall Mean at 72 weeks [SD]	10·6[11·0]	9·9[14·3]	0·97	0·77,1·22	0·81

[a] Adjusted by study centre, gender.

Table 5 - Adverse event reports summary post randomisation

Adverse event report categories	Treatment arm	
	Usual treatment (n=152)	PEPS (n=154)
Participants with any adverse event, N individuals (%)	39(26)	60(39)
All adverse event reports[a], N events (N individuals)		
Hospitalisation	62(33)	100(51)
Death[b]	0	4(4)
Other	14(12)	13(12)
TOTAL	76(39)	117(60)
Participants with multiple hospitalisations, N individuals (%)		
1	19(58)	29(56)
2	6(18)	13(26)
3	3(9)	3(6)
4	4(12)	2(4)
5	0	1(2)
6	1(3)	0
7	0	2(4)
9	0	1(2)
Mental health related adverse event reports, N events (N individuals)		
Planned/respite hospital admission	2(2)	1(1)
Self-harm including drug or alcohol overdose	27(16)	42(24)
Suicide or attempted suicide	4(3)	7(7)
Deterioration in mental health	3(2)	9(7)
Suicidal ideation	6(6)	8(6)
Other	3(3)	4(4)
TOTAL	45(26)	71(37)
Participants with multiple self-harm reports, N individuals (%)		
1	11(69)	16(67)
2	2(12)	3(12)
3	1(6)	1(4)
4	1(6)	3(12)
5	1(6)	1(4)

[a] Some participants reported >1 type of adverse event

[b]Two of the deaths were due to natural causes and two were suicide.

Table 6: Comparisons of the number of individuals with at least one AE, and the total number of reported AEs

			Risk difference		Relative risk		Incidence Rate Ratio	
	Usual Treatment n=152	**PEPS n=154**	**Crude**	**Adjusted[a]**	**Crude**	**Adjusted[a]**	**Crude**	**Adjusted[a]**
Total follow up (person-years)	178	203						
Number (%) of individuals with at least one AE	39 (26)	60 (39)	13·3% (2·9%, 23·7%)	13·0% (2·9%, 23·1%)	1·52 (1·09, 2·12)	1·52 (1·09, 2·13)	1·35 (0·89, 2·07)	1·37 (0·91, 2·05)
Total number of AEs	76	117	--	--	--	--	1·35 (1·00, 1·83)	1·24 (0·93, 1·64)

[a] adjusted by site and gender