



## Extended Research Article

# Treatment effect modifiers of cognitive behaviour therapy in people with psychosis: an individual participant data meta-analysis of RCTs

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## Scientific summary

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# Scientific summary

## Background

Cognitive-behavioural therapy (CBT) is a psychological intervention recommended by the National Institute for Health and Care Excellence (NICE) for the treatment and management of psychosis and schizophrenia. Aggregate data meta-analyses suggest that CBT for psychosis has modest but considerably heterogeneous treatment effects. This inconsistency partly stems from intertrial variation in several key methodological characteristics of the existing randomised controlled trials (RCTs) (e.g. blinding/masking of outcome assessments) but could also reflect the impact of unaccounted-for clinical heterogeneity – that is, specific intervention and patient characteristics that can influence the clinical effectiveness of CBT. For instance, previous trials differed widely in terms of intervention characteristics (e.g. number of sessions, treatment duration, use of manualised interventions), patients' baseline severity of psychotic and other comorbid symptoms, and their demographic characteristics (e.g. age, gender and ethnic origin) and illness duration. The identification of moderators of treatment response and/or subgroups of patients who may particularly benefit from CBT would allow optimisation of treatment delivery, with implications in terms of improved clinical effectiveness, cost savings and maximisation of patients' informed choice of treatment. The impact of these potential treatment effect modifiers, however, remains unaccounted for or at best poorly estimated in meta-analyses of aggregate study-level data due to their reliance on the reporting quality of primary studies and the limited statistical power of 'standard' meta-analytic methods for testing treatment effect moderators. Individual participant data (IPD) meta-analysis, a research synthesis method which summarises the evidence on a particular clinical question by considering individual participant rather than aggregated data from multiple related studies, allows for greater ability to examine the impact of multiple individual-level and study-level factors on the treatment effects considered, and is therefore a method ideally suited for identifying potential treatment effect modifiers of CBT interventions for people with schizophrenia and related psychotic disorders.

## Objectives

The CBTp IMPART (cognitive-behavioural therapy for psychosis/Individual Modifiers of Patient Response to Treatment) project was an IPD meta-analysis which aimed to identify potential treatment effect modifiers of CBT in people with diagnoses on the schizophrenia spectrum.

## Methods

Randomised controlled trials relevant for this evidence synthesis were identified through the literature searches of a recent aggregate data meta-analysis of this research literature (CRD42013003911). In line with the eligibility criteria of the aggregate data meta-analysis, the present IPD meta-analysis included RCTs comparing CBT to treatment as usual (TAU) and/or other active control psychosocial interventions (AC) in individuals with schizophrenia spectrum diagnoses in any setting (i.e. outpatient community settings as well as inpatient hospital settings). The primary outcome of this IPD meta-analysis was overall symptom change as measured by valid and reliable measures of psychotic symptoms severity – that is, the total score of Positive and Negative Syndrome Scales (PANSSs) or comparable measures that could be converted into PANSS total scores via validated conversion algorithms. In addition to this primary outcome, the original secondary aims of the CBTp IMPART project were to examine treatment effect modifiers of CBTp interventions across a range of outcomes frequently considered in eligible trials, including analyses of minimum clinically important differences and clinically significant deteriorations in PANSS scores as well as change in specific symptom clusters (positive symptoms, negative symptoms and general psychopathology symptoms), specific symptoms often targeted in CBTp interventions (hallucinations severity, delusions severity, hallucination-related subjective distress, delusion-related subjective distress, paranoia severity), affective symptoms (anxiety and depression severity), subjectively defined recovery, quality of life, social and occupational functioning, hospital readmissions and recorded adverse effects.

The data owners [i.e. the corresponding authors/data custodians of RCTs of CBT in patients with schizophrenia carried out in the United Kingdom (UK) and worldwide] of 110 trials identified from literature searches conducted in February 2018 as part of the above-mentioned aggregate data meta-analysis were contacted to request access to their trial data sets, with further contacts informed by a subsequent update of the above searches in January 2019. Data owners were also invited to share, when available, additional documentation that could inform or expedite data checking, cleaning and analysis (e.g. relevant IPD metadata, statistical analysis plans, intervention protocols/manuals and/or descriptions of the CBT interventions evaluated in their eligible trials). IPD data sets received by the project team underwent a range of standard quality and consistency checks of the data, including cross-checking the reanalysed IPD against previously published trial results to highlight inconsistencies or possible errors. Data were cleaned wherever necessary and then standardised to allow pooling and subsequent combined analyses of the data. The primary trial reports of all RCTs for which IPD were sought were assessed for risk of bias (RoB) using the Cochrane Collaboration RoB tool, in order to evaluate potential differences between the characteristics of trials that were included in the CBTp IMPART analyses, and trials for which IPD could not be retrieved.

Due to time and resource constraints, the analyses included in the current report focus only on the planned primary outcome analyses (PANSS total scores) using a two-stage IPD analytic approach; the execution of a one-stage IPD meta-analysis of the primary outcome and all secondary outcome analyses will be undertaken in future and reported elsewhere. Longitudinal mixed-effects models containing treatment effect were fitted to the PANSS total score trajectories within each study, allowing all recorded follow-up PANSS measurements to contribute to the model. Pooled treatment effects and confidence intervals (CIs) for the primary outcome were then estimated using a series of two-stage IPD random-effect meta-analyses across four treatment comparisons: CBT versus TAU, CBT versus other psychosocial interventions/active comparisons, CBT integrating additional active elements from other therapies (CBT+) versus TAU, and CBT+ versus AC. Treatment effect modifiers were examined within each treatment comparison by including treatment-covariate interactions in relevant models which were synthesised using random-effects meta-analysis. The list of covariates considered in CBTp IMPART analyses was informed by patient and public involvement and engagement consultations conducted at the project design stage with individuals with lived experience of psychosis and NHS psychological practitioners. The covariates tested included several participant-level variables considering participants' demographic characteristics (age at trial entry, gender, ethnicity) and participants' clinical characteristics [illness duration, phase of illness (first episode of psychosis vs. multiple episodes), duration of untreated psychosis, initial severity of psychotic symptoms, initial severity of affective symptoms, number of antipsychotic medications at baseline], as well as study-level variables pertaining to specific characteristics of the CBT interventions considered in the included trials (treatment duration, number of therapy sessions, level of therapists' training/competence, use of manualised interventions, formulation-based interventions, individual vs. group interventions).

## Results

Data from 53 trials were provided by the contacted data owners, collectively considering a total of 5952 randomised participants (i.e. 48.0% of the 110 trials approached and 54.0% of the total IPD). The retrieved data sets pertained to trials predominantly conducted in the UK, whereas the trials for which IPD could not be included in the CBTp IMPART analyses were from a broader range of countries. The RoB assessment suggested that the included trials had a different overall RoB profile compared to trials that were not retrieved or could not be included in the CBTp IMPART analyses. Specifically, the included trials presented significantly lower risk for selection bias, detection bias, and attrition bias.

A total of 27 trials ( $n = 2870$ ) were available for the planned CBT versus TAU primary outcome analyses, 11 trials ( $n = 961$ ) for the CBT versus AC analyses, 14 trials ( $n = 1985$ ) for the CBT+ versus TAU analyses and 3 trials ( $n = 235$ ) for the CBT+ versus AC analyses. However, a smaller volume of IPD was available for trials that specifically provided data relevant to the primary outcome analyses and provided data for more than one follow-up point in order to fit the planned longitudinal mixed-model analyses (16 trials with 2089 randomised participants for the CBT vs. TAU comparison; 8 trials with 819 randomised participants for CBT vs. AC; 6 trials with 924 participants for CBT+ vs. TAU; 3 trials with 235 participants for the CBT+ vs. AC).

The main treatment effect analysis for the CBT versus TAU treatment comparison indicated CBT is associated with significant reduction in PANSS scores (mean difference  $-2.93$ , 95% CI  $-4.18$  to  $-1.68$ ) across all follow-ups compared to TAU, with a reasonably consistent direction of treatment effect across the included studies ( $I^2 = 38\%$ ). The main effect analyses for the remaining treatment comparisons did not find evidence of a significant clinical benefit of CBT when compared to AC, or CBT+ interventions when compared to TAU or AC. The treatment by covariate interaction analyses found no reliable evidence indicating that the variables considered in this IPD meta-analysis significantly moderated the effectiveness of CBT in this patient group.

## Conclusions

The findings of the CBTp IMPART analyses corroborate the efficacy of CBT interventions compared to TAU evidenced in previous aggregate data meta-analyses of this research literature. While the reduction in PANSS scores observed in the present analyses is modest even when compared to the summary treatment effects of past aggregate data meta-analyses, this is a likely by-product of the analytic approach used in this IPD evidence synthesis, which aimed to utilise all available follow-up data considered in the included trials, as opposed to the more conventional approach involving the estimation of a summary treatment effect at a single follow-up point (e.g. end of treatment or the closest available follow-up following end of treatment). Conversely, our IPD meta-analysis found no evidence of superiority of CBT interventions compared to other active psychosocial interventions. While this finding is consistent with literature suggesting that different empirically validated psychotherapies may be equally effective, our results are incongruent with the findings of another recent IPD meta-analysis that focused specifically on RCTs comparing CBT interventions to other psychological interventions in people with psychosis, which led to findings in support of the superiority of CBT for improving overall psychotic symptom severity. This incongruence may be due to the different analytic approach employed in these IPD meta-analyses, as well as differences in the IPD data sets that were respectively retrieved and included in these two IPD evidence syntheses.

Unlike previous meta-analyses of this research literature, but in line with the approach taken in the aggregate data meta-analysis that informed the CBTp IMPART project, in the present IPD evidence synthesis we differentiated between trials considering CBT interventions fully consistent with the criteria outlined by current NICE guidelines for the treatment and management of schizophrenia and related psychoses, and trials that considered intervention packages that comprised both CBT and additional treatment components derived from other discrete psychological interventions, that is, the 'CBT+ versus TAU' and 'CBT+ versus AC' treatment comparisons. The analyses conducted as part of the CBTp IMPART project suggest that CBT+ interventions are not associated with significant reductions in PANSS scores across subsequent follow-ups relative to comparator treatments (TAU and AC, respectively). However, caution should be exerted when interpreting these findings, in particular relative to the treatment effect of 'purer' CBT intervention protocols outlined in the above-mentioned analyses, as these results may be due to the considerably lower number of trials (and IPD) available for the analyses for the CBT+ versus TAU and CBT+ AC treatment comparisons, as well as the extreme heterogeneity of the 'CBT+' interventions included in this treatment comparison, which may therefore not be linked to a consistent treatment effect.

Pertaining to the main objective of the project – that is, the identification of treatment effect modifiers of CBT interventions – the results of the treatment by covariate interaction analyses suggest that none of the variables examined as part of this IPD meta-analysis represent robust or reliable moderators of the efficacy of CBT interventions in people with diagnoses on the schizophrenia spectrum. In line with these findings, the principal clinical recommendation arising from this evidence synthesis is that CBT should continue to be offered equally to all service users with psychosis irrespective of their demographic characteristics, their clinical characteristics or the severity of their mental health difficulties, in line with current NICE recommendations. While the current IPD evidence synthesis did not identify treatment effect modifiers of CBT interventions in people with schizophrenia spectrum diagnoses, several factors may have limited our ability to identify variables that could maximise or account for heterogeneity in the effectiveness of CBT. First, while the current project represents the largest IPD meta-analysis of this research literature, it was not possible to retrieve a considerable proportion of the IPD that would have been relevant to the analyses planned as part of the CBTp IMPART project, therefore potentially limiting our ability to identify small or moderate treatment effect moderators in certain analyses. Second, while our analytic approach attempted to consider important

variances in the characteristics of the CBT interventions that have been thus far evaluated in available RCTs, the CBT intervention protocols evaluated in this body of clinical trials are highly heterogeneous, for example in terms of their modular structure, components, exact intervention strategies and treatment targets. The work conducted as part of this IPD meta-analysis was not designed to examine whether these more subtle variances in intervention characteristics may be associated with differences in CBT effectiveness. Hence, other potential avenues for examining whether these intervention-related characteristics may be associated with CBT efficacy could be explored as part of future research: for example, approaches that could enable the more fine-grained examination of the efficacy of specific intervention components within CBT intervention protocols, and analyses comparing existing more 'traditional' CBT protocols to newer intervention protocols that have shown evidence of improved efficacy in recent research, such as treatment protocols informed by 'interventionist-causal paradigms' which specifically target, using CBT intervention strategies, psychological mechanisms allegedly involved in the formation and maintenance of specific psychotic symptoms.

Further learning from the CBTp IMPART project is more broadly related to the process of conducting IPD meta-analyses of complex psychological interventions in clients with serious mental health difficulties. The data collection, data management and the cleaning and recoding of IPD proved more challenging than anticipated, and required considerably more time and resources than initially projected. Several initiatives could be implemented to facilitate and expedite future large-scale secondary analysis projects and IPD meta-analyses in this clinical research area, including the development and implementation of core outcome sets suited for the evaluation of psychological interventions in people with schizophrenia and related psychosis to facilitate outcome pooling across trials, the further promotion of use of trial data repositories and data-sharing practices to expedite access to relevant IPD, and the implementation and curation of detailed metadata documentation to facilitate data reuse.

## Study registration

This study is registered as PROSPERO CRD42017060068.

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## This article

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