National Institute for Health Research

For whom is Cognitive Behavioural Therapy (CBT) for psychosis most effective? An IPD meta-analysis of randomised control trials comparing CBT versus standard care and other psychosocial interventions (Cognitive Behaviour Therapy for Psychosis: Individual Modifiers of Patient Response to Treatment)

Protocol

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1. Summary of Research

Cognitive behavioural therapy (CBT) is a NICE-recommended intervention for the treatment and management of psychosis and schizophrenia [1]. Aggregate data meta-analyses suggest that CBT for psychosis has modest but considerably heterogeneous treatment effects. This inconsistency partly stems from inter-trial variation in several key methodological characteristics of the existing randomised controlled trials (for example, blinding/masking of outcome assessments [2, 3]) but could also reflect the impact of unaccounted clinical heterogeneity i.e. specific intervention and patient characteristics that can potentially 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, their demographic characteristics (e.g. age, gender and ethnic origin) and illness duration. The identification of moderators of treatment response and/or sub-groups of patients who may particularly benefit from CBT would allow optimisation of treatment delivery, with significant 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 of the reporting quality of primary studies and the limited statistical power of "standard" meta-analytic methods for testing treatment effect moderators [4]. Additional primary research would be costly and impractical given the likely large sample size required. A more efficient approach suited for this type of research is 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. Individual participant data meta-analyses allow for greater ability to examine the impact of multiple individual-level and study-level factors (and their combination) on the treatment effects considered, standardisation of statistical methods used across studies, and the potential of reduced risk of bias e.g. due to selective reporting of outcomes compared to conventional aggregate data meta-analysis [5-8].

The research will identify treatment effect modifiers of CBT in people with diagnoses in the schizophrenia-spectrum using IPD meta-analytic methods. This evidence synthesis will consider randomised controlled trials (RCTs) comparing CBT to standard care or other psychosocial interventions in individuals with a diagnosis of schizophrenia-spectrum disorders. In line with the analytic approach employed in recent aggregate data meta-analyses [9, 10] our IPD evidence synthesis will distinguish between trials which considered "pure" CBT interventions as defined by NICE [1] and trials which considered "CBT+" interventions, where CBT+ is defined as a CBT treatment packages that incorporated significant elements of other, distinct psychosocial intervention approaches (e.g. mindfulness, motivational interviewing, family intervention) alongside core CBT elements. The primary outcomes will be overall symptoms change as measured by valid and reliable measures of psychotic symptoms severity (i.e. the Positive and Negative Syndrome Scales or comparable measures [11-13]).

This evidence synthesis will build on and update the literature searches of a recent aggregate data meta-analysis conducted by members of our team [9, 10]. We will obtain relevant IPD through a collaborative network we have established (the CBTp: IMPART Consortium), which comprises the

principal investigators/data custodians of RCTs of CBT in patients with schizophrenia carried in the UK and worldwide. Pooled treatment effects and confidence intervals will be estimated using a series of two-step IPD random-effect meta-analyses [5, 6]. We will then examine the effect of potential treatment effect modifiers, which will include participants' demographic (age; gender; ethnicity), participants' clinical characteristics (dosage equivalence of baseline anti-psychotic medication; number of anti-psychotic medications received at baseline; effect of specific diagnostic subgroups; phase of the illness e.g. first episode psychosis vs multiple episodes; illness duration; duration of untreated psychosis; initial severity of psychotic symptoms; initial severity of comorbid affective symptoms specifically anxiety and depression) and characteristics of the CBT interventions evaluated in eligible RCTs (treatment duration; number of therapy sessions offered by the study; minimum study required level of therapists' training and competence; use of manualised interventions, use of formulation-based interventions; treatment modality [individual or group]). Treatment effect modifiers will be examined by testing treatment by covariate interactions in relevant models [5, 6]. The findings of this evidence synthesis will be interpreted in the light of risk of bias assessments and consideration of impact of IPD unavailability.

2. Aims and Objectives

2.1 - Primary objective

The primary objective of this evidence synthesis will be to identify, using IPD meta-analysis, the treatment effect modifiers of CBT and CBT+ on overall psychotic symptoms severity in patients with schizophrenia-spectrum diagnoses when compared to 1) standard care and 2) other psychosocial treatments.

The treatment modifiers examined will include participants' demographic characteristics (age; gender; ethnicity), participants' clinical characteristics (dosage equivalence of baseline anti-psychotic medication, number of anti-psychotic medications received at baseline; effect of specific diagnostic subgroups; phase of the illness e.g. first episode psychosis vs multiple episodes; illness duration; duration of untreated psychosis; initial severity of psychotic symptoms; initial severity of comorbid affective symptoms specifically anxiety and depression), and specific intervention characteristics (treatment duration; number of therapy sessions offered by the study; minimum study required level of therapists' training and competence; use of manualised interventions, use of formulation-based interventions; treatment modality [individual or group intervention]). The selection of

candidate treatment modifiers was informed by 1) our knowledge of the variables examined in previous and on-going RCTs by members of our team and the collaborators who joined the CBTp: IMPART Consortium; 2) the findings of the (limited) studies which examined predictors of outcomes in previous RCTs [e.g. 14, 15-17], and 3) consultation meetings with service-users with psychosis (the Psychosis Research Unit Service User Reference Group, located within Greater Manchester Mental Health NHS Mental Health Foundation Trust), and clinical psychologists and CBT therapists working with clients with psychosis in NHS secondary care settings in several Greater Manchester NHS Trusts.

3. Evidence synthesis strategy

This evidence synthesis will follow state-of-the-art guidelines for IPD meta-analytic syntheses, and our outputs will comply as a minimum with the PRISMA statement for the reporting of IPD meta-analysis [8]. The search strategy of our IPD meta-analysis builds on the protocol and database searches carried out as part of a recent meta-analysis of aggregate data carried out by members of our team [9, 10]. Our study selection criteria are consistent with those employed in this recent aggregate data evidence synthesis. Similarly, our literature searches will update those carried out as part of this review to identify any RCTs that have become available since the date of search.

3.1 - Search Strategy

Eligibility criteria

The following selection criteria will be used:

Population: Trials where > 50% of participants have diagnoses in the schizophrenia-spectrum (schizophrenia, schizoaffective disorder or early psychosis) will be eligible. Trials where > 50% participants have an established diagnosis of bipolar disorder, intellectual disability, psychosis secondary to a general medical condition or organic pathology, or a primary diagnosis of substance-induced psychosis will be excluded. No restriction will be placed on participants' age, ethnicity, illness severity and illness duration.

Intervention and Comparators: Trials will be eligible if they evaluated CBT or CBT+ interventions versus standard care or other psychosocial treatments. Consistent with NICE definitions [1], CBT will be defined as a discrete psychological intervention (i.e. that is in addition to, or separate from, other interventions) where service users:

1) Establish links between, thoughts, beliefs, perceptions and feelings in relation to their current or past symptoms and/or functioning, and
2) Re-evaluate their beliefs, perceptions and reasoning relating to target symptoms;

and that should involve:

3) Service users monitoring their own thoughts, feelings or behaviours with respect to the symptom or recurrence of symptoms, and/or
4) The promotion of alternative ways of coping with the target symptom, and/or
5) Reduction of distress, and/or
6) Improvement of functioning.

We will define CBT+ as CBT treatment packages that incorporated significant elements of other, distinct psychosocial intervention approaches (e.g. mindfulness, motivational interviewing, family intervention) alongside core CBT elements.

Eligible comparators will be standard care (the level of care service users would routinely receive had they not been involved in the trial) and other psychosocial interventions (i.e. where standard care is supplemented by additional psychological or social interventions; e.g. family therapy). Although all trials of CBT against these comparators will be eligible, these will be synthetized and contrasted in separate analyses for 1) CBT versus standard care 2) CBT versus other psychosocial interventions 3) CBT+ versus standard care 4) CBT+ versus other psychosocial interventions.

Study design: Single-blind or open controlled trials utilizing random allocation to treatment will be included. Studies employing other research designs (case series, cross over studies, cohort analyses) will not be eligible.

Outcomes: Our IPD evidence synthesis will focus on the most common primary outcome considered in previous and ongoing RCTs i.e. overall psychotic symptom severity. Publication of analyses pertaining to these outcome is not an eligibility criteria as relevant IPD, even if unpublished, will be requested from primary investigators and data custodians. For these outcomes, we will examine whenever possible both overall outcome change as well as clinically significant improvements and reliable symptom deteriorations using established operational definitions [18-20].

Primary outcome: Our primary outcome will be overall psychotic symptom severity. Hence, we will request IPD comprising continuous and/or binary post-treatment data on valid and reliable measures of overall psychotic symptoms (e.g. overall scores on the Positive and Negative Syndrome

Scales or PANSS [11] and the Brief Psychiatric Rating Scale [13]) at any and all time-points. We will also conduct additional analyses to examine minimum clinical important improvements (MCIDs) in overall positive symptom severity operationally defined using the PANSS. As no widely agreed consensus exists in the literature, we will carry out these analyses using different operational definitions estimated in previous relevant research conducted in the context of antipsychotic medication trials (i.e. 10, 11 and 15 point reductions as per [21, 22]).

Identifying studies - information sources: We will update the searches already conducted as part of a recent meta-analysis of aggregated data [9, 10] to identify any trials that might have been become available for research synthesis since the date of last search. Database searches will be conducted on the Cochrane Central Register of Controlled Trials (CENTRAL), PubMed, EMBASE and the online clinical trials registers of the US government, European Union, World Health Organization and Current Controlled Trials Ltd.

Identifying studies - electronic searches: In line with the protocol of the aggregate meta-analysis carried out by members of our team [9, 10], titles, abstracts and keywords will be searched in the publication databases using the adaptations of following generic strategy:

(schizo$ [exp. schizophrenia + psychosis + schizoaffective]) AND (trial [exp. RCT +controlled trial + clinical trial]) AND (cbt [exp. cognitive therapy + behaviour therapy +psychotherapy]).

Study selection process: The project's PI and another member of the research team will screen titles and abstracts for relevance, and subsequently assess eligibility by examining the full-text reports against the above-mentioned criteria. When required, additional information to ascertain eligibility will be requested from the RCTs' authors and through the examination of treatment manual when available (e.g. to ascertain that interventions complied with NICE operational definitions of CBT). Discrepancies in selection decisions will be discussed, and arbitration by other members of the research team sought to achieve consensus.

IPD data collection: IPD will be collected from principal investigators of eligible RCTs. Our ability to successfully collect relevant IPD is facilitated by several factors. Our research team includes researchers who have conducted some of the largest RCTs in this area. Furthermore, we have established a network of collaborators to support the retrieval of relevant IPD: the CBTp IMPART Consortium. We will continue to expand the CBTp IMPART Consortium over the lifetime of the project by sending invitation emails to all researchers who have published and/or are currently conducting randomised controlled trials relevant to this work. Participating researchers will be sent specific data request forms outlining variables pertinent to the present evidence synthesis. They will

be asked to fully anonymise the requested dataset and share them with our research team using a safe data transfer system provided by the University of Liverpool. We will remain in regular contact with all Consortium members throughout the lifetime of the project to clarify queries about their IPD and its integrity.

Data items: All data received will be systematically recoded to ensure common scales or measurements across studies. We will liaise with principal investigators and statisticians of the primary studies to resolve any data issues and prepare the dataset for IPD-meta-analysis. In addition to outcomes data, IPD and relevant supporting material (e.g. protocol, dataset codebook/specification documents, therapy manuals, statistical analysis plans) will be requested to code the following variables as possible treatment effect modifiers of CBT for psychosis:

1) Participants' demographic characteristics (age; gender; ethnicity)
2) Participants' clinical characteristics (effect of specific diagnostic subgroups; phase of the illness e.g. first episode psychosis vs multiple episodes; illness duration; duration of untreated psychosis; initial severity of psychotic symptoms; initial severity of comorbid affective symptoms i.e. anxiety and depression, dosage equivalence of baseline anti-psychotic medications, and number of anti-psychotic medications received at baseline)
3) Characteristics of the CBT intervention (measures of therapeutic alliance; treatment duration; number of therapy sessions offered by the study; number of therapy sessions attended by the patient; minimum study required level of therapists' training and competence; use of manualised interventions, use of formulation-based interventions; whether the intervention was designed to target the outcome under scrutiny; treatment modality [individual vs group intervention]; duration of follow-up).

A statistical analysis plan detailing the data cleaning and coding, and the analyses to be conducted has been produced and will be available upon request.

Risk of bias assessment in individual studies: We will assess risk of bias with the Cochrane Collaboration Risk of Bias tool (version 5.2.0). The results of this assessment will be used to inform interpretation and overall conclusions of our research findings.

Effect measures: Where an outcome or variable can be recorded on multiple scales, attempts will be made to transform to the most commonly recorded scale where the scales are comparable. If transformation to a common scale is impossible, standardised values (calculated by dividing by the between patient variation) will be employed. Details of data preparation are given in the Statistical Analysis Plan.

3.2 Data Analysis / Synthesis Method

Full details of data analysis are given in the Statistical Analysis Plan.

Analyses of the overall treatment effect: We will include all randomised patients, and the intention to treat (ITT) principle will be followed throughout. To examine IPD integrity and concordance with original trial analyses, all trials will be re-analysed individually and the original authors asked to confirm the individual study results and resolve any discrepancies. We will examine the pooled treatment effect by performing a series of two-step IPD meta-analyses (where estimates of the treatment effect are initially computed from the IPD of each study, and then aggregated using conventional meta-analytic methods) [5]. We will employ a random effects approach. In two stage analyses, statistical heterogeneity will be examined using the 'tau-squared' statistics (which provides an estimate of between-study variance) and I^2 (which provides the proportion of total variance that is due to "true" heterogeneity in treatment effects).

Due to considerable variation in the follow-up periods considered in the original trials, separate analysis of trials with highly comparable or identical points of assessment (e.g. 3 month, 6 month etc.) would be unfeasible. Instead, in order to maximise the data contributing to the analysis, we will employ methods that include the longitudinal measurement as far as possible. For outcomes not measured repeatedly over time, we will employ methods appropriate to the type of data supplied (e.g. generalized linear models for continuous scores or binary scores measured at a single time point). The treatment effect estimate produced by this analysis will represent the treatment effect across the whole time period.

Analyses of treatment effects modifiers: To examine treatment effect modifiers, we will estimate treatment-moderator interactions following a two-step analysis approach (by estimating treatment-moderator interactions within each study followed by a standard inverse variance meta-analysis) [5, 6]. Our IPD meta-analysis will involve examining multiple treatment modifiers. The examination of multiple comparisons/testing is an under-researched area with no accepted standards in IPD meta-analysis. We consider these issues unproblematic in the context of the study as our analyses of the treatment modifiers of CBT will be, to an extent, exploratory (given the paucity of reliable findings on predictors of outcome in primary studies). In all cases, we will take multiple comparisons/testing issues into account during the judicious interpretation of our research findings, and explore the implementation of any novel methodological development/recommended standard that might become available over the duration of the project.

Examination of potential sources of bias: As mentioned, we will assess risk of bias in each study with the Cochrane Collaboration Risk of Bias tool (version 5.2.0). Results will be interpreted in light of the risk of bias of the studies included in the meta-analysis. Publication bias (and other selection bias/small study effects) will be investigated through inspection of contour-enhanced funnel plots and appropriate statistical tests for funnel plot asymmetry [23-25]. These procedures will be restricted to analyses comprising 10 or more trials, due to the low power of these bias assessment procedures in meta-analyses including small number of trials. IPD meta-analysis may be affected by sources of bias that are generally not applicable to conventional meta-analysis, more specifically the possible presence of systematic differences between the obtained IPD and trials for which IPD is not available. To assess for the presence of such bias, we will compare characteristics and the results of our risk of bias evaluation between studies for which IPD was retrieved and studies for which IPD was unavailable. The findings of our IPD research syntheses will be interpreted (and when possible adjusted) in the light of the above bias analyses.

4. Publication policy

In addition to the HTA report, the findings of this evidence synthesis will be published as series of papers in peer-reviewed journals. Group authorship on all outputs will be offered to the members of the CBTp: IMPART Consortium who will provide IPD for this evidence synthesis.

5. Conflicts of interest

We recognise that one member of our team may be regarded as having a vested interest in CBT (Morrison is the only co-applicant actively involved in CBT training, leading of trial grants and receiving royalties from CBT texts or books), but other members of the team do not have similar conflicts of interest. The protocol has been developed with input from and under the close supervision of an IPD meta-analysis expert, Tudur Smith, who has no vested interested in the efficacy of CBT. Our project management plan includes multiple steps through which Tudur Smith will actively input in the execution and monitoring of this project ensuring that the work will be undertaken rigorously and with integrity. All data management activities and statistical analyses will be undertaken by a research associate (Sudell) at University of Liverpool under the supervision of Tudur Smith; the statistics team at the University of Liverpool was not involved in any of the previous trial of CBT for psychosis.

6. Changes to the protocol

Version 2.0 of the protocol reflects changes made to expedite the delivery of the primary outcome analyses of the IMPART project. These were ultimately due to the impact of a range of extenuating circumstances experienced by the project team over the course of this evidence synthesis, including but not limited to the impact of the COVID-19 pandemic. These resulted in a reduced capacity to complete the extensive data management activities originally planned within the timeframe of the project, ultimately leading to a collaborative decision with the Funder to focus on the high-quality delivery of the analyses addressing the primary research question of the review (i.e. analyses considering our pre-specified primary outcome). The current protocol reflects the decision to omit planned analyses of secondary outcomes as described in previously approved versions of the protocol, as well as the examination of certain treatment effect modifiers due to limited data availability. Other adjustments include a reduced set of subsidiary analyses to further expedite the delivery of the primary outcome analyses. These decisions were not influenced by results of any analyses of the secondary outcomes originally considered in the planned synthesis (i.e. these outcomes were not analysed). Secondary outcome data that have collected as part of the IMPART project (as per protocol version 1.10) may be considered in future secondary analysis work by the project team, should there be capacity.

Funding acknowledgement:

This project was funded by the NIHR Health Technology Assessment Programme (project number 15/187)

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