Improving Outcomes for People with Psychosis in Pakistan and India – Enhancing the Effectiveness of Community-Based Care (PIECEs)

Statistical Analysis Plan (SAP)

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Contributors to Analysis Plan

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Contents

List of Abbreviations

SAP	Statistical Analysis Plan
PIECEs	Pakistan and India-Enhancing the Effectiveness of Community-Based Care
ISRCTN	International Standard Randomised Controlled Trial Number
RCT	Randomised Controlled Trial
QoL	Quality of Life
MANSA	Manchester Short Assessment of Quality of Life
UBACC	University of California Brief Assessment of Capacity to Consent
QMUL	Queen Mary University of London
SCARF	Schizophrenia Research Foundation
JPMC	Jinnah Postgraduate Medical Centre
KeH	Karwan-e-Hayat
ICD	International Classification of Diseases
ICC	Intra-cluster correlation coefficient
PPDA	Proposal and Partnership Development Award
REDCap	Research Electronic Data Capture
CONSORT	Consolidated Standards of Reporting Trials
SOP	Standard Operating Procedure
BPRS	Brief Psychiatric Rating Scale
SANS	Scale for the Assessment of Negative Symptoms
HAS	Helping Alliance Scale
WHODAS	WHO Disability assessment Schedule
BAS	Burden Assessment Scale
CSRI	Client Service Receipt Inventory
IQR	Interquartile Range
SD	Standard Deviation
ITT	Intention-to-treat
MI	Multiple Imputations
MAR	Missing At Random
CI	Confidence Interval
MICE	Multivariate Imputation via Chained Equations
AEs	Adverse Events

1. Administrative Information

Trial registration number: ISRCTN Registry – ISRCTN13022816

This SAP is based on the PIECEs protocol version V2_21 April 2022 (date 21st, April 2022) - Link

SAP revision history

Protocol version	Updated SAP version no.	Section number changed	List of changes from previous version/protocol	Author of change	Date
2.0	1.0	2,3,4,5,7	Adapted to PIECEs protocol	MY	26-7-2023
2.0	2.0	3,4,5,7	Adjustments to PIECEs instruments	MY	7-8-2023
2.0	2.1	4,5,7	Proposed changes to primary and secondary analyses	MY	8-8-2023
2.0	3.0	2,4,5,7	Changes to timelines for primary and secondary analysis and criteria for mITT design	MY	11-10-2023
2.0	3.1	2,4,5,7	Edits to sample size, randomization details and tables	MY, OQ	24-10-2023
2.0	3.12	2,3,4,5,7	Changes to statistical analyses approach across different sections	VB	14-11-2023
2.0	3.13	1,2,3,4,5,6,7	MY made changes made to sample size, analysis, tables, abbreviations, background and references upon VB and ZMT's feedback. ZMT made significant contributions to the SAP.	MY, ZMT, OQ	14-12-2023
2.0	3.2	1,2,3,4,5,6,7	References updated, Sample size justification, Analysis focusing ITT, removed per-protocol section to bring more clarity, Tables updated	MY, OZ	06-02-2024

*If the SAP has been published, indicate which version.

Members of the writing committee
Maryam Younus wrote the first and second draft of the Statistical Analysis Plan (SAP). Zaw Myo Tun contributed to the third draft.

Timing of SAP revisions in relation to unblinding of data/results
The statisticians remained blinded until this SAP was completed prior to database lock (at which point treatment allocation will be revealed).

Remit of SAP

The purpose of this document is to provide details of the statistical analyses and presentation of results to be reported within the principal paper(s) of the PIECEs RCT. Subsequent papers of a more exploratory nature, including those involving baseline data only, will not be bound by this strategy but will be expected to follow the broad principles laid down in it. Any exploratory, post hoc or unplanned analyses will be clearly identified in the respective study analysis report.

2. Background and Trial Design

Study objectives	Primary objective: To assess the effectiveness of DIALOG+ in improving quality of life at 6 months, measured by MANSA, for the patients diagnosed with psychosis. Secondary objectives: To assess the quality of life at 12 months and symptoms, treatment satisfaction, physical health, and social situation for the people diagnosed with psychosis at 6 and 12 months.
Study design	This is a cluster-randomised controlled trial study with embedded process evaluation.
Study setting	The study will be conducted at one urban site in Chennai, India (the SCARF outpatient clinic) and two urban sites in Karachi, Pakistan (Jinnah Postgraduate Medical Centre and Karwan-e-Hayat).
Participants	**Inclusion criteria** For clinicians: - Aged 18 years or over - Regularly sees individuals with psychosis in clinical practice - Self-reported experience of working with individuals with psychosis - No plans to leave the current post within the next six months. For patients: - Aged 18-65 years old - Diagnosis of psychosis defined as an ICD-10 diagnosis of Schizophrenia, schizotypal, delusional, and other non-mood psychotic disorders (F20-29) and/or bipolar disorder with psychotic features (F31.2, F31.5, F31.64) - Currently not receiving inpatient treatment - Duration of illness greater than two years - Score <5 on Manchester Short Assessment of Quality of Life (MANSA) - Capacity to provide informed consent - Ability to speak and understand the local language - Randomised to the intervention arm (process evaluation only)

	For Caregivers: – Primary caregiver of a person with psychosis enrolled in the DIALOG+ RCT (primary caregiver defined as the main person responsible for helping with activities of daily living, supporting, and advocating on behalf of the person) – Has been the primary caregiver of a person with psychosis for more than 6 months – Aged 18-75 years old – Ability to speak and understand Urdu, Tamil or English **Exclusion criteria** For clinicians/Caregivers: - Does not have regular contact with individual(s) with chronic psychosis - Unable to speak either Urdu or Tamil For patients - Conditions resulting in an individual's inability to provide consent (a diagnosis of dementia and/or significant cognitive impairment and/or severe learning disability, organic psychosis or drug-induced psychosis, or - UBACC score $\leq$ 12
Interventions	Control arm: Clinicians will be trained on the DIALOG scale and will deliver care as usual. During the course of each monthly meeting, patients will rate their satisfaction with 11 different areas (8 life domains and 3 treatment domains) on the DIALOG scale but will not discuss their ratings with their clinician. Intervention arm: Clinicians will be trained in the use of DIALOG+. Patients will use DIALOG+ in monthly meetings, to structure their routine meetings and rate their satisfaction with different life and treatment domains and then discuss the ratings with their treating clinician using the DIALOG+ intervention, following the principles of solution-focused therapy.

	DIALOG+ will be delivered in addition to usual care.

3. Sample Size and Randomisation

Sample size Estimation

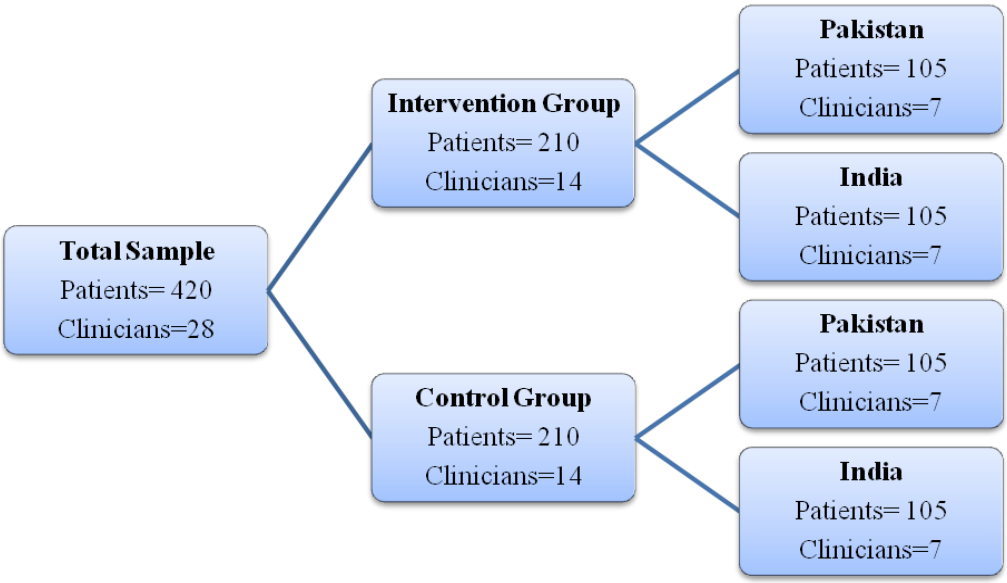
For this multi-center, cluster randomized controlled trial (RCT), we aimed to achieve 90% statistical power at 5% significance level to detect a medium effect size of 0.5 (Priebe et al., 2017). We also assumed an intra-cluster correlation coefficient (ICC) of (ρ=0.002), as observed in the DIALOG+ trial. We incorporated a conservative design effect of 1.03(Bird et al., 2023).

The study will be conducted in one urban site in Chennai, India (SCARF outpatient clinic), and two urban sites in Karachi, Pakistan (Jinnah Postgraduate Medical Centre and Karwan-e-Hayat).

The total number of patients required in each country is 84 per group (n=168 per country). After allowing for a drop-out rate of 20%, a total of 210 patients were recruited to give the analysable sample of 168 or 84 per group. Therefore, 28 clinicians (14 in each country) were recruited, with an average of 15 patients per clinician.

This design and recruitment strategy was devised to ensure the robustness and validity of our study within the context of a multi-center, cluster RCT. For the calculation of sample size online calculator for Means-Sample size calculator/clustered https://sample-size.net/means-sample-sizeclustered/ was utilised, assuming individual randomisation is inflated by a design effect (DE) to reach the required level of statistical power under cluster randomization (Rutterford et al., 2015).

Design effect= 1 + ρ(m-1); where m= Cluster size; ρ= ICC



Flow chart of study sample

Clinicians of any background, including lay community workers, were eligible. Meetings held within each of the participating clinical services during the proposal and partnership development award (PPDA) indicated that there were sufficient clinicians in each site to carry out the intervention and with the intention to stay in employment during the period of the trial. In a brief scoping survey in our pilot study, we found that more than 14 clinicians were employed and available to support the trial (Bird et al., 2022). Individual clinicians were the unit of randomisation. Clinicians were randomised to either the intervention or control arm at a 1:1 ratio when they met either of the following conditions:

1. There are 15 patients under their care for each clinician are recruited
2. Fewer than 15 patients recruited but three months have elapsed since the enrolment and baseline assessment of their first patient

Randomisation Procedure

Clinicians are recruited from three sites across the two countries (SCARF outpatient clinic [Chennai, India]; Jinnah Postgraduate Medical Centre; and Karwan-e-Hayat [Karachi, Pakistan]). Patients with psychosis who are receiving care from the included clinicians and their primary caregivers are recruited. Participants will complete quantitative measures at baseline after 6 and 12 months following randomisation.

Clinicians and their respective cluster of patients are randomised into a treatment and active control arm. The total duration of the intervention is 12 months from the date of randomisation. Randomisation is performed by the RCT Manager Sana Sajun (SS) at QMUL through the 'Block Randomisation' method using a centralised computer system in QMUL. In this method, clusters are divided into 4 blocks of a fixed size before randomisation. This was done on a country by country basis. The allocation status of clinicians is known to the project manager and unblinded members of the research team who need to know the allocation to help with RCT session coordination. There are at least two unblinded researchers per trial site. All other researchers are blind to allocation.

For the cluster RCT, 14 mental health professionals are recruited from the outpatient clinic at each of the included clinical sites. The caseloads of mental health professionals are screened by researchers and supported by members of the clinical team, if required, to identify potentially eligible patients. Our aim was to recruit, on average, 15 patients with psychosis per mental health professional.

Potentially eligible patients who agreed to being approached by a researcher were given information about the study. Researchers have then met with eligible participants to sign a consent form and complete the eligibility screening. This has involved completing the MANSA, where only individuals with a score of 5 or below were eligible to continue with the study.

Caregivers of enrolled RCT patients are approached and provided information about the study. Researchers have checked the eligibility and interest to join the study in order to understand the impact DIALOG+ has on the caregiving burden for people who have relatives living with psychosis.

4. General Analysis Considerations

Data Management

All research data was captured using Research Electronic Data Capture (REDCap) (Harris et al., 2009) tool. Redcap is a secure, web-based application designed to support data capture for research studies. It provides an intuitive interface for data entry, audit trails for tracking data manipulation and export, automated export procedures for downloads to statistical packages, and procedures for importing data from external sources. The lead investigators and study coordinators at each site check and clean the research data.

CONSORT numbers

We have described the number of study participants who went through the trial in a CONSORT flow chart in Appendix 3.

Timing of Analysis

Research data will be analysed after the endline data collection (i.e. 12 months after the baseline assessment) estimated by March '24. Before analysing the data, it will be ensured that data collection on REDCAP (Harris et al., 2009) is completed, the data quality meets the requirements of the Data Cleaning SOP (version 1.1), and that the SAP document is finalised and approved by the study PI Prof. Victoria Bird.

No formal interim analyses have been planned for the trial data.

Analysis Populations

Intention-to-treat (ITT) analysis will be used as the main analysis (ITT analysis is used as the main analysis when the proportion of missing outcome in the overall data is over 5%). (Jakobsen et al., 2017) Analysis will be based on the participants who have been assigned into DIALOG/DIALOG+ group post randomisation following the baseline assessment visit. All recruited patients with recorded outcomes will be included in the analysis. Also, patients with missing outcome data will be included if their outcomes can be imputed based on other available data (explained further in the section below).

Missing Data Imputation

The imputation of missing outcome data will be based on treatment arms, clinician clusters and covariates (sites, Age, Gender, and baseline MANSA score), including the same outcome at earlier time points (where applicable), with a random component-based on univariate regression imputation model using the MICE (Multivariate Imputation via Chained Equations) command in R statistical package. It assumes the missing values will be missing at random (MAR).

While conducting MI, a choice will be made about the number of imputations to perform. This will depend on the precision required in estimation. A simple rule of thumb is to use one imputation (m=1) per percent of missing data (Cro et al., 2020).

When analysing using the ITT population, model-based multiple imputations (MI) will be used for both primary and secondary outcomes. Distribution plots or descriptive statistics will be created to check the accuracy of the imputations.

Sensitivity Analysis

We will conduct sensitivity analyses to assess whether the imputed data are reasonable and to evaluate the impact of missing outcome data on the results of the main analysis (ITT). We will impute the missing data of the following outcome measures assuming data missing at random (MAR):
(i) The primary outcome: MANSA score at 6 months
(ii) The secondary outcomes: MANSA score at 12 months SIX, BPRS, SANS, HAS, ED-5Q-5L, WHODAS 2.0, HAS (Therapist version), Burden Assessment Scale scores at 6 and 12 months.

Results and estimates from sensitivity analysis will be compared against those from the actual data analysis.

Outcome Measures

Primary:

Manchester Short Assessment of Quality (MANSA) score of patients at 6-month post randomization. MANSA is a measure for assessing subjective quality of life (Priebe et al., 1999). It consists of 16 items, of which 4 carry dichotomous responses and 12 use a 7-point Likert scale, from 1: could not be worse to 7: could not be better. Quality of life of patients will be assessed based on a total score of 12 questions.

Secondary:

Post baseline scores of the following are the secondary outcomes of the study.

Patients

- Manchester Short Assessment of Quality (MANSA) score of patients at 12-month post randomization.
- Brief Psychiatric Rating Scale (BPRS) score of patients at 6 and 12 months. It consists of 24 symptom constructs, each to be rated in a 7-point scale of severity ranging from 'not present' to 'extremely severe' If a specific symptom is not rated, mark 'NA=0' (not assessed). Sum of the total 24 items will be reported.
- Scale for the Assessment of Negative Symptoms (SANS) score of patients at 6 and 12 months. The SANS is a 24-item clinician-administered questionnaire, which divides symptoms into five subscales within each subscale it rates separate symptoms from 0 (absent) to 5 (severe). Sum of 24 items will be reported.
- Objective Social Outcomes Index (SIX) score of patients at 6 and 12 months. The simple sum of scores across all items ranges from 0-6. The score indicates social outcomes in an objective manner. Sum of items will be reported.
- Helping Alliance Scale (HAS) I (Client/patient version) score of patients at 6 and 12 months. The HAS score at all time points will be calculated as the total of scores on 6 -item.
- Health Questionnaire (EQ-5D-5L) scores of patients at 6 and 12 months. The EQ-5D-5L descriptive system comprises the following five dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension has 5 levels: no problems, some problems, of middle range, of severe range and extreme problems.
- WHO Disability assessment Schedule 2.0 (WHODAS 2.0) scores of patients at 6 and 12 months. WHODAS-2.0 includes 12 items covering different domains of functioning. Each item used a five-level scale with 1 denoting “no difficulty” and 5 denoting “extreme difficulty or cannot do.” The simple sum of item scores across all domains constitutes a statistic that is sufficient to describe the degree of functional limitations.
- No. of Hospitalizations, self reported by patients.

- Client Service Receipt Inventory (CSRI) of patients. CSRI is a tool used to collect information on the whole range of services and supports study participants may use. e.g. Average time(minutes) spent in meetings with health care professionals, services used, number and types of mental and physical health professionals seen.

Clinicians

- Helping Alliance Scale II (Therapist version) score of Clinicians at 6 and 12 months. The HAS score at all time points will be calculated as the total of scores on the 7-item HAS questionnaire.

Caregivers

- Burden Assessment Scale score of Caregiver at 6 and 12 months (used in the Pakistan trial sites). The BAS score is calculated as the total of scores on a 19-item questionnaire. Each item is rated on a 4-point scale (1 = not at all; 4 = a lot). To score the BAS, ratings from each item are added together to give a total score, with higher scores indicating greater levels of caregiver burden.
- Burden Assessment Schedule for Caregiver (used in the Indian trial sites) score of Caregivers at 6 and 12 months. BAS is a 40-item structured instrument which assesses both the objective and subjective burden experienced by the caregiver of chronic mentally ill patients.

5. Statistical Analysis

An independent statistician blinded to allocation status of clinicians and participants will analyse the data. We will present a summary of the session attendance by treatment arm for the whole study population including a correction for loss to follow-up.

Baseline demographics, clinical characteristics, and baseline assessments of all the primary and secondary outcomes of patients, caregivers, and clinicians will be summarised for each treatment arm by the mean and standard deviation for continuous variables and the frequency and percentage for categorical variables. The draft **(Tables 1–3)** is presented in Appendix 1.

All outcomes will be presented using descriptive statistics: normally distributed data by the mean and standard deviation (SD) and skewed distributions by the median and interquartile range (IQR). Binary and categorical variables will be presented using counts and percentages. All analyses will be conducted as two-sided, with significance interpreted at the 5% level.

All analyses will be carried out using the R statistical package.

Main Analysis

The data will be analysed based on the intention-to-treat (ITT) approach: patients of both DIALOG and DIALOG+ arms who have attended their baseline assessment visit will be analysed according to the treatment arm assigned following randomisation. A **mixed-effect linear regression model** will be used to assess the effect of intervention (DIALOG+) on the MANSA score at 6 months from baseline (equation below). Treatment arms will be included as fixed effect, clinician clusters will be considered random effect, and the baseline MANSA score will be adjusted as a covariate (fixed effect) in the model. The estimated difference in mean MANSA score between treatment arms at 6 months, corresponding 95% confidence interval (CI), and significance value (P-values) will be presented **(Table 4).**

$$y=X\beta+Z\gamma+\varepsilon$$

Where y is a vector of responses, X is the fixed effects design matrix, β is a vector of fixed-effects parameters, the extra term $Z\gamma$ models the random effects. Z is the design matrix of random effects and $\gamma$is a vector of random-effects parameters. ε is a vector of residual errors.

In lay terms:

Mixed effect model = Fixed effect (Treatment arms + Covariate/s) + Random effect (Clinicians Clusters)

Secondary and Additional Analyses

We will also perform the following additional analyses.

Secondary outcomes Analysis

We will use mixed-effects linear regression models to assess the effect of DIALOG+ on secondary outcomes (see 'Outcome measures' section above for more details) at 6 and 12 months from baseline. The model specification will be the same as the primary outcome analysis (ITT) above and will also compare between study groups using a mixed-effects linear regression model except for the adjustment of the baseline score; we will adjust for the baseline score of the corresponding outcome measure. **(Table 5)**

Adjusting for covariates

To assess the robustness of the primary result to the possible influence of "nuisance" factors, the MANSA analysis will be repeated including in addition to the original specification the following list of covariates: Age, gender, site, Country, No. of session attended, baseline MANSA-score etc. Imputation of covariates will be carried out to substantiate analysis if missingness is present to a degree greater than 5%. The treatment effect estimated from this analysis will be reported and compared against the primary analysis.

Longitudinal Analysis

A linear mixed effects model will be conducted with MANSA scores and other secondary outcomes at all time points as the dependent variable. The model will include treatments as fixed effect, random effect for clusters (Clinicians) and cross-classified random effects of time and patient. In this way, treatment is estimated under the assumption that data are missing at random conditional on the included data. The associated table **(Table 5)** can be found in Appendix 1.

Sub-group Analysis

We will perform a subgroup analysis for each country to assess the impact of interventions on outcomes on imputed data. **(Table 6)**

Per-protocol Analysis

To assess the treatment effect under treatment fidelity, a per-protocol analysis will also be carried out on MANSA scores, using the same methods as the main analysis (on ITT population) but including only those patients who were randomised and attended at least 2 sessions. A mixed effects linear

regression will be conducted for collected data (not imputed data) in order to observe the discrepancy between the results of ITT and per protocol analyses.

Safety Monitoring

Serious adverse events (SAEs) that are "related" and "unexpected" will be reported according to regulations of the Research Ethics Committee (REC) and other relevant regulations in India and Pakistan. Adverse events (AEs) will be reported as per the PIECEs Adverse Events and Serious Adverse Events SOP (Version 2.0), from the point of enrolment until the end of the patient's participation. Data from AE forms will be extracted to summarise the adverse events using the template in **(Table 7)**. The number of (i) SAEs and (ii) participants experiencing at least one SAE will be reported by the treatment arm. In addition, the percentage as a total of eligible patients in the treatment group will be reported for the second of these presentations.

6. References

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7. Appendices

Appendix 1: Tables for Statistical Analysis

Table 1 – Demographic Characteristics - Patients

For all Numerical variables mean (SD) presented, N (%) for all categorical variables

Participant demographics	Summary Measure		Missing Data	
	Intervention Group	Control Group	Intervention Group	Control Group
Age (years); Mean(SD)				
Gender; N (%)				
Male				
Female				
Other				
Country; N (%)				
Pakistan				
India				
Site; N (%)				
JPMC				
KEH				
SCARF				
Marital Status; N (%)				
Single/unmarried				
Married/cohabiting/civil partnership				
Separated/divorced				
Widow/widower				
Country of Birth; N (%)				
Pakistan				
India				

Other				
First Language; N (%)				
Urdu				
Tamil				
Telugu				
.....				
Highest completed level; N (%)				
No formal education				
Primary education or less of education				
Matriculation				
Intermediate/A-Levels				
Higher education (e.g. University)				
Vocational / Skills based training				
Madarsah based education				
Other				
Year of completed education; Mean(SD)				
Accommodation type; N (%)				
Independent accommodation				
Supported accommodation (nursing home)				
Homeless / roofless				
Other accommodation				
Current living situation				

Living alone				
Living with a partner or family				
Living with friend(s)				
Living in shared accommodation				
Employment Status; N (%)				
Paid or self-employment (full time)				
Paid or self-employment (part time)				
Voluntary employment (unpaid)				
Sheltered employment				
Unemployed				
Student				
Housewife/husband				
Retired				
Other				
Ethnicity; N (%)				
Punjabi				
Sindhi				
Balochi				
Pashto				
Urdu				
Tamil				
.....				

Mental Health diagnosis; N (%)				
Primary diagnosis (ICD-10)				
Duration of receiving treatment for severe mental illness(in years); Mean(SD)				
Previous Psychiatric Hospital admission; N (%)				
Yes				
No				
Means of transport; N(%)				
Public				
Private / Rental				
Own / Borrowed				
Were you accompanied by anyone during your last visit?;N(%)				
Yes				
No				
Relationship of the person accompanying you for this visit?;N(%)				
Husband				
wife				
.....				

Table 2 - Demographic Characteristics- Caregiver

Participant demographics	Summary Measure		Missing Data	
	Intervention Group	Control Group	Intervention Group	Control Group
Age (years); Mean(SD)				
Gender; N (%)				
Male				
Female				
Other				
Marital Status; N (%)				
Single/unmarried				
Married/cohabiting/civil partnership				
Separated/divorced				
Widow/widower				
Relationship to patient (ID); N(%)				
Parents				
Spouse				
Siblings				
Child				
Aunt/Uncle				
Nephew/Niece				
Cousin				
Friend				
Other				

Duration of living with the patients (in yrs.); Mean(SD)				
Duration of Caregiving (in yrs.); Mean(SD)				
Highest completed level; N (%)				
No formal education				
Primary education or less of education				
Matriculation				
Intermediate/A-Levels				
Higher education (e.g. University)				
Vocational / Skills based training				
Madarsah based education				
Other				
Employment Status; N (%)				
Paid or self-employment (full time)				
Paid or self-employment (part time)				
Voluntary employment (unpaid)				
Sheltered employment				
Unemployed				
Student				
Housewife/husband				
Retired				
Other				

Are you taking treatment of any mental health conditions?; N(%)				
Yes				
No				
If yes; How long(years); Mean(SD)				
Are you taking treatment of any physical health conditions?; N(%)				
Yes				
No				
If yes; How long(years); Mean(SD)				

Table 3 - Demographic Characteristics- Clinicians

Participant's demographics	Summary Measure		Missing Data	
	Intervention Group	Control Group	Intervention Group	Control Group
Age (years);N(%)				
<35 years				
35-49 years				
50-65 years				
>65 years				
Gender; N (%)				
Male				
Female				
Other				
Professional Background; N(%)				
Psychiatrist				
Psychologist				
Psychiatric student				
Other				
Current job role; N(%)				
.....				
.....				
Year of experience as a clinician; Mean(SD)				
Year of experience as working within mental health; Mean(SD)				

Ethnicity; N(%)				
Punjabi				
Sindhi				
Balochi				
Pashto				
Urdu speaking				
Other				

Table 4: Primary Analysis- Mixed factors effect on the MANSA score at 6 months in psychosis patients

Primary Outcomes	Intervention		Control		Unadjusted Effect Estimate (95% CI); P-value	Adjusted Effect Estimate (95% CI); P-value
	N	Mean+/-SD	N	Mean+/-SD		
Baseline MANSA score						
MANSA score at 6 months-Patients						

Unadjusted estimates are mean differences of the outcome between groups.
Adjusted estimates for fixed and random effects: clinician as random effects, treatment groups and covariate (Baseline MANSA score) as fixed effects. Using mixed-effect linear regression models.
P value less than 0.05 as significant.

Table 5: Secondary and Longitudinal Analysis- Mixed factors effect on the study Outcome

Secondary Outcomes	Intervention		Control		Unadjusted Effect Estimate (95% CI); P-value	Adjusted Effect Estimate (95% CI); P-value	P-value (Longitudinal Analysis)
	N	Mean+/- SD	N	Mean+/- SD			
MANSA score at Baseline-Patients							
SIX score at 6 months-Patients							
SIX score at 12 months-Patients							
WHODAS score at Baseline-Patients							
WHODAS score at 6 months-Patients							
WHODAS score at 12 months-Patients							
EQ-5D-5L score at Baseline-Patients							
EQ-5D-5L score at 6 months-Patients							
EQ-5D-5L score at 12 months-Patients							
Helping Alliance Scale-Client version at Baseline-Patients							
Helping Alliance Scale-Client version at 6 months-Patients							
Helping Alliance Scale-Client version at 12 months-Patients							
BPRS at Baseline-Patients							
BPRS at 6 months-Patients							
BPRS at 12 months-Patients							
SANS at Baseline-Patients							
SANS at 6 months-Patients							
SANS at 12 months-Patients							
Burden Assessment Scale score at Baseline-Caregivers							

Burden Assessment Scale score at 6 months-Caregivers							
Burden Assessment Scale score at 12 months-Caregivers							
Burden Assessment Schedule score at Baseline-Caregivers							
Burden Assessment Schedule score at 6 months-Caregivers							
Burden Assessment Schedule score at 12 months-Caregivers							
Helping Alliance scale score at Baseline-Clinicians							
Helping Alliance scale score at 6 months-Clinicians							
Helping Alliance scale score at 12 months-Clinicians							

Unadjusted estimates are mean differences of the outcome between groups.
Adjusted estimates for fixed and random effects: clinician as random effects, treatment groups and covariate (Baseline MANSA score) as fixed effects. Using mixed-effect linear regression models.

Table 6: Sub-group Analysis - Primary Outcome

Outcomes	Intervention		Control		Unadjusted Effect Estimate	Adjusted Effect Estimate
	N	Mean/-SD	n	Mean/-SD	(95% CI); P-value	(95% CI); P-value
Primary Outcome						
MANSA score at 6 months						
Sub-group 1- Pakistan						
Sub-group 2- India						

Unadjusted estimates are differences in mean outcome between groups.
Adjusted estimates for fixed and random effects: clinician as random effects, treatment groups and covariate (baseline MANSA score) as fixed effects. Using mixed-effect linear regression models.

Table 7- Adverse Events related to the PIECEs Trial

Adverse Events	Intervention	Active Control
Adverse events n (%)		
Adverse event 1		
Adverse event 1		
Etc…		

Appendix 2: Example R Codes for Analyses

Packages for Multiple Imputations

```
library(mice)
library(VIM)
library(lattice)
library(ggplot2)
library(mi)
md.pattern(dataset)
mice_plot <- aggr(dataset, col=c('navyblue','red'), numbers=TRUE, sortVars=TRUE, labels=names(dataset), cex.axis=.7, gap=3, ylab=c("Histogram of missing data","Pattern"))#visual presentation of missing data
dataset1 <- dataset[, c("MANSA@6month", "sites", "Age", "Gender", "baseline MANSA score") #create subset of variables to either impute or use as predictors for imputation.#
imp <- mice(dtaset1, m = 5, print = FALSE, seed = 12345)
imp
m1.mi <- with(imp, lm(MANSA_6 ~ selected covariates))
summary(pool(ml.mi))
imp <- mice(data, method = "norm.predict", m = 5) # Impute data
data_det <- complete(imp) # Store imputed data
```

Packages for Mixed effect models

```
library(ggplot2)
```

```
library(GGally)

library(tidyverse)

library(ggfortify)

library(ggpubr)

library(lme4) # linear mixed effect model

library(lmerTest)
```

 # Fit linear regression#

For Unadjusted linear effect regression model

```
mod1 <- lm(MANSA @ 6 month ~ study_group, data = dataset)

autoplot(mod1)

summary(mod1)
```

 # Mixed-effect linear regression model#

For mixed-effects regression model using the lmer function from the lme4 package with clinician clusters as a random effect.

```
Mod2 <- lmer(MANSA_6m ~ study_group + baseline MANSA+ (1 | clinician) , data = dataset)

autoplot(mod2)

summary(mod2)
```

 # Mixed-effect linear regression adjusted model#

```
Mod3 <- lmer(MANSA_6m ~ study_group + baseline MANSA+ Age + gender + site + Country + (1 | clinician) , data = dataset)

autoplot(mod3)

summary(mod3)
```

Appendix 3: Study Flow (CONSORT) Chart