Health Economics Analysis Plan (HEAP)

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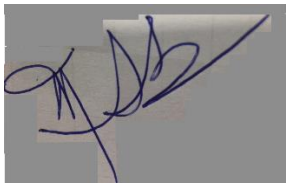
Administrative details

Title	Economic Evaluation Analysis Plan for PIECEs Trial: Assessing the effectiveness and cost-effectiveness of a solution-focused resource-orientated approach (DIALOG+) to improving the quality of life for people with psychosis, a cluster randomized control trial in India and Pakistan
Trial registration number	ISRCTN13022816
Source of funding	National Institute for Health Research (NIHR)
Purpose of HEAP	The HEAP describes the analysis and reporting plans related to the economic evaluation of PIECEs RCT. It should be read in conjunction with the trial protocol and associated statistical analysis plan.
Trial protocol version	Protocol v9.0, 30.SEP.2021
Trial Statistical Analysis Plan (SAP) version	SAP v1.0, 03.MAR.2023
Trial HEAP version	HEAP v1.Dec.2023
HEAP revisions	Details of the HEAP revision are separately presented at the end of this table.
Roles and responsibilities	The HEAP is developed by Ashar Malik, Assistant professor (Health Economics), Dr Malik is responsible for conducting and reporting the economics evaluation of PIECEs RCT in accordance with the HEAP.
Signature of Health Economist	Dr Muhammad Ashar Malik  10/12/2023

Signature of Principal Investigator	Professor Dr Victoria Jane Bird  30/12/2023

Chapter 1 Project Description

Background: Improving community-based mental health care in India and Pakistan (PIECEs) is a research project funded by the National Institute of Health Research, Research and Innovation for Global Health Transformation (RIGHT) program (NIHR200824), which runs from September 2020 to February 2025[1]

PIECEs is a collaboration between the Unit for Social and Community Psychiatry (Queen Mary University of London), Schizophrenia Research Foundation (SCARF – Chennai, India) and Interactive Research and Development (IRD – Karachi, Pakistan), in partnership with the London School of Economics (LSE), Warwick University and Aga Khan University. [2]

PIECEs has five work packages covering wide-ranging research projects including formative qualitative research a large-scale randomized controlled trial of a low-cost intervention, and involvement of local communities and healthcare providers via arts-based methodologies. Work Package 2 is a multi-country cluster randomised control trial (RCT) aiming to assess the effectiveness of DIALOG+ for the management of psychosis in resource-poor settings of India and Pakistan. The PIECEs trial is being conducted in three field sites, two in Pakistan and one in India.

Objective of the trial: The Cluster RCT has three main objectives:[3]

1. To test the effectiveness of DIALOG+ as compared to an active control in improving the quality of life, clinical and social outcomes for individuals with long-term psychosis receiving community-based care in India and Pakistan.
2. To assess the cost-effectiveness of DIALOG+.
3. To understand the experience and acceptability of DIALOG+ within routine services in India and Pakistan

Intervention and control: The RCT tests DIALOG+: a low-cost app-mediated intervention that invites the patient to rate their satisfaction with eight life domains and three treatment aspects. DIALOG+ is a specific intervention that uses the DIALOG scale to provide a comprehensive overview of a person's life, followed by a brief four-step solution-focused intervention that helps the patient identify resources to develop solutions to any concerns raised (London Mental Health Transformation Programme).[4] The control arm of the RCT is the active control where the patient rates their satisfaction on the DIALOG Scale only, without any further discussion. During the six months that make up the active intervention phase, both the DIALOG scale and the DIALOG+ intervention will be used once a month.

Trial Settings: The PIECEs Trial is conducted in India and Pakistan at three healthcare providers. In Pakistan it includes two urban locations in Karachi, —one outpatient clinic at a sizable public hospital (Jinnah Postgraduate Medical Centre) and an outpatient clinic at a private mental

health facility (Karwan-e-Hayat)—and in India, — one urban outpatient clinic in Chennai, India (Schizophrenia Research Foundation - SCARF).[3]

Trial Design and blinding: The design of the trial is a cluster randomized controlled trial. After considering the findings of a pilot study, which guided the intervention's local modification, the cluster RCT's design was completed. The mental health professionals who will be recruited from outpatient clinics at three included clinical sites will serve as the unit of analysis for the RCT. In every site, permuted blocked randomization will be employed, with block sizes of m=4 and 2. An impartial statistician at QMUL will perform randomization using computer-generated random numbers to decide allocation. A 1:1 ratio will be used to allocate participants to control and intervention groups.[3]

Sample size. The sampling strategy of the PIECES RCT includes 210 participants in each country across both arms in 14 clusters per country (28 in total) of the RCT (Bird, 2018). Figure 1 provides the description of sample size.

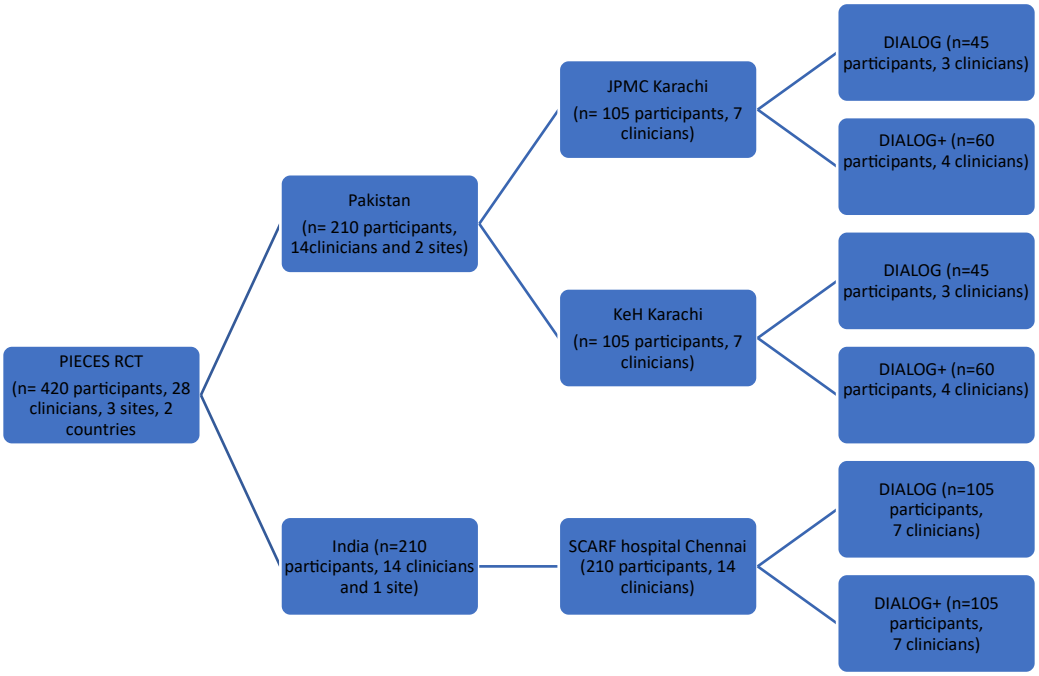


Figure Design of Multi-country multiple site PIECEs RCT

Software and IT support: Data collection and analysis in the cluster RCT will rely on recommended data management and analytical tools. The RCT database will be managed using RedCap (Research Electronic Data Capture) software provided by Vanderbilt University Medical Center. Additional data management will be conducted using Microsoft . Analysis of data will be carried out using both Microsoft Excel and Stata version 17 provided by Stata Corporation LLC.

Chapter 2 Economic Evaluation Design

The economic evaluation component of the PIECEs trial will provide evidence on the cost-effectiveness of the DIALOG+ intervention in India and Pakistan separately. The RCT will recruit clinicians from three sites across two countries: SCARF outpatient clinic, Chennai, India; and Jinnah Postgraduate Medical Centre and Karwan-e-Hayat in Karachi, Pakistan. Patients with psychosis who are receiving care from these clinicians will be recruited for the study. Participants will complete quantitative measures at baseline and again at 6- and 12-months following randomization. In the following text we provide the analysis plan of the economic evaluation component of the PIECEs RCT.

As customary to full scale economic evaluation of health interventions, there will be two arms to compare their costs and their respective outcomes. The outcomes will be measured as gains in quality and length of life measured through Quality Adjusted Life Years. The cost components will include the costs to individuals and their families and the costs to the healthcare providers for the addition of DIALOG+ to the routine management of psychosis.

Aim and objective: The economic evaluation component of the PIECES RCT aims to assess the cost effectiveness of DIALOG+ in India and Pakistan.

Perspective of analysis: The health system, which includes patients and their families, is the viewpoint used in the economic evaluation. This viewpoint is in line with the goals and parameters of our research, which is to assess a low-cost intervention that can be provided by non-specialist healthcare providers and integrated into current health systems. This perspective was taken due to the lack of social institutions that support the needs of people with serious mental illness outside of healthcare.

Type of Analysis: We will perform a cost-utility analysis, in which the economic costs and the quality of life of the results are estimated. Estimates of patient and health system costs will be provided. Quality Adjusted Life Years will be the primary outcome of the analysis. We have selected QALYs because they enable us to compare the cost-effectiveness of the intervention with other therapies for different domains and to measure the impact of the intervention on both the physical and mental health domains.[5] We will also explore reporting cost-effectiveness analysis because clinical effectiveness data will be gathered specifically tailored to our context of managing psychosis with DIALOG+. A cost-effectiveness analysis will be helpful in comparing DIALOG+'s efficacy in the clinical setting of managing psychosis. Cost-Utility Analysis, however, enables such comparisons with treatments in the broader spectrum of health beyond specific clinical outcomes to include overall health benefits and quality of life improvements.[5]

Time Horizon: The six-month RCT implementation period and the subsequent six-month follow-up are included in the one-year time horizon of the economic evaluation.

Choice of Comparator: The intervention arm, DIALOG+, and the active control arm, DIALOG, are the two arms of the RCT. During routine meetings with clinicians, participants in the

intervention arm get treatment in two stages. Firstly, a structured patient assessment (DIALOG) covering satisfaction (Likert scale of 1-7) in eleven dimensions (eight life domains and three treatment domains).[6] The patient's issues are then addressed using a four-step solution-focused treatment (+ component) method. Using a tablet or smartphone, the intervention is given during regular appointments. Patients in the control arm will complete the DIALOG scale at the conclusion of each session, without any discussion or completion of the four-step solution-focused component, to account for the addition of a tablet computer in the consultation and for repeated quality-of-life assessments.[6] Patients recruited in the RCT will continue to receive standard treatment including routine meetings with clinicians, as the intervention is delivered during routine consultations.

Geographical Jurisdictions: The Cost Utility Analysis will be carried out separately in each country. The objective of this strategy is to inform the local level decision making within each country and to aid priority settings. Pooled analysis for the RCT will be carried out to help understand the cost-effectiveness of DIALOG+ in resource poor settings in LMICs. Such analysis will help generalizability of the economic evidence beyond geographical jurisdiction.[7]

Costs: The costs in the economic evaluation will include the resources allocated within the trial. Three cost centers are as follows: a) resources related to healthcare facilities, such as utilities, supplies, and time spent by mental health professionals and other medical and support staff providing care; b) resources used by patients and their carers to seek healthcare, such as travel expenses, lodging expenses, and lost productivity; and c) resources related to conducting the RCT, such as staff training, incentives for the clinicians, and tablets for using the DIALOG application, among other things.

Unit costs for the services are not readily available in any of the three sites involved in the RCT. This situation is common in many low and low-middle-income countries, where traditional costing methods are infrequently used in healthcare decision making and where health insurance mechanisms or other third-party payment systems are still developing[8] To overcome this challenge, a separate exercise will be carried out to capture the resource use through a Time and Motion Study and collection of facility level data on the prices of inputs involved in the delivery of health services. Ethical approval has been obtained for these addendums to the RCT protocols.

Time and Motion Study: Time and motion studies are helpful to track resources employed on health procedures and contribute to efforts to improve the efficiency of health systems.[9] Facility level resources use will be estimated by a time and motion study (TMS) nested on a sub-sample of the PIECEs RCT. The study aims to estimate the resources used for the provision of the intervention namely DIALOG+ and its active control (DIALOG scale only) during the RCT at the health facilities. This will be an observational cross-sectional study with a purposive sample n=180 participants (Table 1).

Table 1 Sampling Strategy for the Time and Motion Study

Total	Total Sample 180 participants of RCT		
Country	India (60)	Pakistan (120)	
Facility	SCARF	Karwan-e-Hayat	JPMC
	10 active control (5 women and 5 men) and 10 interventions (5 women and 5 men at each interval	At each interval (10 active control (5 women and 5 men) and 10 intervention (5 women and 5 men)	(10 active control (5 women and 5 men) and 10 intervention (5 women and 5 men)
	Baseline=20	Baseline=20	Baseline=20
	6 months follow up=20	6 months follow up=20	6 months follow up=20
	12 months follow up=20	12 months follow up=20	12 months follow up=20
RCT arm	50% active control (Dialog scale) and 50% Intervention (Dialog +) (90 participants in active control (30 in India and 60 in Pakistan) and 90 participants in intervention (30 in India and 60 in Pakistan))		
Gender	50% female (90 participants)		

Facility level Data collection: A data collection questionnaire is developed for the three sites of PIECEs RCT. This tool includes a section on details of staff salaries, prices of inputs and supplies, expenditure of the hospital on utilities etc. The data collection period of this exercise is the financial year when the RCT is implemented in both countries i.e. 2023.

Outcomes: The outcomes will be based on improvement in quality of life captured by the generic instruments and will be reported as Quality Adjusted Life year. For this purpose, we will

use EQ5D – 5L provided by the EuroQoL research group.[10] The valuation of EQ5D-5L will be drawn from locally available studies in both countries explained in the next chapters.[5]

Chapter 3 Data Collection and management

Data collection and management at RCT:

The RCT data will be collected by the trained data collectors and will be stored in RedCap. Both cost and outcomes data will be collected at baseline, primary endpoint at six months, and follow-up at 12 months of the RCT.

Data on health-related quality of life will be drawn from the EQ-5D 5L - a generic instrument for assessing quality of life in five areas is the EQ5D 5L: mobility, self-care, regular activities, pain/discomfort, and anxiety/depression. There are five levels for each dimension: none, minor, moderate, severe, and serious difficulties. The EUROQOL group provides the EQ5D 5L versions in Tamil and Urdu.

The expenses incurred by the patient and carer for healthcare consultations include travel expenses to the medical institution, lost productivity, and cash expenses on prescription drugs, laboratory work, and other out-of-pocket expenses. Three sources will be used to collect data for patients and carer resources: a modified Client Services Receipt Inventory (CSRI), a visit information questionnaire, and a socioeconomic and demographic questionnaire. In conjunction with data from the visit information questionnaire (i.e., number of visits; accompanying persons) and the CSRI (to estimate the number of working days lost), the socio-economic and demographic questionnaire will capture use of outpatient healthcare services and inpatient care.

Table 2 provides data collection schemes in the RCT framework.

Table 2 Data collection scheme for the economic evaluation in PIECEs RCT

Type	Cost centre	Instrument	Unit/ Data Source	Data collector	Frequency of Data Collection	Data Storage
Resource Use	Patient and caregiver costs	Client Service Receipt Inventory (CSRI)	Patient	Researcher	Thrice (Baseline, six months, and 12 months	RedCap
	Health facility costs	TMS data collection sheet	Facility	Researcher	Twice (Baseline, six months)	Manual/MS Excel

		Facility data collection questionnaire	Facility	Researcher	Once	Manual/MS Excel
	RCT intervention cost	Quarterly Expenditure Report and Expense Claims forms	International Research Management QMUL	Economic Analyst	Once	Manual/MS Excel
Outcomes	Health related quality of life	EQ-5D-5L	Patient	Researcher	Thrice (Baseline, six months, and 12 months)	RedCap
	Mean item score	Manchester Short Assessment of Quality of Life (MANSA)	Patient	Researcher	Thrice (Baseline, six months, and 12 months)	RedCap
Socio-Demographic and other stratifies	Basic demographic data including gender, age, ethnicity, marital status, education etc.	Basic Demographic Form	Patient	Researcher	Once (Baseline)	RedCap

Provider costs: The resources used by healthcare providers include all inputs provided by the health facilities to deliver services to the participants in the PIECEs RCT. This includesthe time

spent by medical staff, the use of waiting rooms and consultation clinics, as well as supplies, instruments, and equipment used during consultations at the relevant health facility. To accurately capture these data, we will employ two distinct methodologies: the Time and Motion Study (TMS) and the Health Facility Level Data Collection. These are designed to systematically gather comprehensive data regarding the utilization of resources in health facilities.

Among the RCT participants, a subsample of 180 will provide the data for the TMS. Gender, health facility, and data collection intervals are used to stratify the sample, which consists of 60 participants (20 people at baseline, six months, and 12 months). To estimate how long research participants spend at the medical facility for the patient visit, an unblinded data collector will time them using a stopwatch from the time they check in until they depart the consultation clinic.

The financial and administrative records of healthcare institutions for the fiscal year 2022–2023 will be the source of the data at the health facility level. This will comprise spending information on the resources used at the health facility level to provide healthcare services, such as pay for medical, nursing, and support workers as well as expenses related to fixed assets, utilities, and other supplies. Each healthcare facility was given access to a custom Microsoft Excel tool designed for gathering pertinent data about them. The information gathered will be used to calculate how much a patient's visit to a psychiatry clinic will cost the health facility.

RCT inputs: The resources for the RCT comprise healthcare practitioners' training on DIALOG+, supply of tablet computers and incentives to the healthcare practitioners recruited at the RCT. The expenditure statement of the PIECEs grant housed with the Unit of Social Psychiatry at Queen Mary University of London, as well as the quarterly expense reports of the RCT's implementation partners, will be the sources of the data on intervention costs and active control. The Table gives an overview of the instruments used for data collection as well as the frequency of data collection. All information will be gathered by qualified researchers.

Chapter 4 Methods of Data analysis

Using local currencies (INR and PKR, respectively) and to estimate QALYs with country-specific value sets for EQ5D 5L, we will do a primary analysis at the national level for India and Pakistan separately. In the next step we will also perform a pooled analysis reporting costs in US dollars (USD) or/and British Pounds (GBP), and a shared value set for EQ5D 5L for both countries. We will use the most recent suggestion from the Taskforce on Consolidated Health Economic Evaluation Reporting Standards (CHEERS) to report the analysis's findings.[11]

Unit Costs Analysis: At the patient level, the expenses of the three different resource types—patient/caregiver, health facility, and RCT resources—will be aggregated. We will utilize semiparametric bootstrapping techniques to account for noise caused by participant demographic features, clustering by the type of healthcare facility to increase the generalizability of healthcare providers' costs arising from the fact that these will be drawn from a subsample of PIECES RCT participants.

Date, price, currency, and conversion: For audiences in India and Pakistan, respectively, the local cost-effectiveness analysis will be given in Indian Rupees (INR) and Pakistani Rupees (PKR). The prices for 2022–2023 will include a report on all resource utilization. The official inflation rates for Pakistan and India will be used to raise the costs of earlier years to those of the present year.

Estimating QALYs: Applying the population preferences (values established) for other studies, to EQ5D 5L data will provide estimate QALYs. To estimate QALYs for the PIECES RCT's Indian field site, Jyani and Sharma et al.'s (2022) value set of EQ5D 5L will be consulted. Time trade-off from a population-representative sample (n = 3548) is used to generate this value set, which includes the Tamil area (the PIECEs RCT research site) for geographical representation. For Pakistan, We will use the values specified on the EQ5D 3L provided by Malik and Gu et al (2023). [12] We will leverage the three-level EQ5D values set for Pakistan together with the techniques reviewed by van Hout and Janssen et al. (2012) to obtain a value set for EQ5D 5L.[13]

Reporting results: We shall present the findings of the economic evaluation as incremental cost-effectiveness ratios (ICERs). The ICERs will be calculated by dividing the cost differences between DIALOG+ and DIALOG by the QALY difference.[5] The difference between the patient's QALYs while receiving DIALOG+ treatment and their QALYs when receiving active control DIALOG will also be used to estimate the incremental QALYs.

Accounting for variability and uncertainty: By measuring the intra-cluster correlation coefficient, we will investigate the extent of clustering caused by nesting in data across clinicians. In addition, we will investigate the use of multiple linear regression models and/or multi-level models to identify variations in the differential cost in the two arms of the PIECEs RCT. ~~Regression models in India will incorporate RCT participants who are exclusively concentrated among physicians.~~

We will take into consideration several factors that contribute to the differences in estimated ICERS between India and Pakistan, including hospital reimbursement and formulary decisions, healthcare provider incentives, and patterns of healthcare finance. These factors are derived from the pooled economic evaluation for both nations. To account for clustering within nations or jurisdictions, we shall investigate suitable models. The estimates of incremental cost, incremental effects, and ICERs from OLS linear regression with fixed effects of health facility and country indicators and a Hierarchical linear model that considers data nesting at the country, health facility, and patient-specific factors like gender will be compared in the robustness check.[14]

The robustness of the reported mean costs, incremental costs, incremental QALYs, and incremental cost-effectiveness ratios will be tested using one-way and two-way sensitivity analysis. [15] There are several factors that could lead to uncertainty, such as the assumptions made when estimating healthcare facility expenditures or the use of the generalizing EQ5D 3L value set for EQ5D 5L. We will rely on the statistical techniques applied to the PIECEs RCT data analysis to address missing or censored data that are provided in the Statistical Analysis Plan for PIECES RCT.[16] For instance missing data will be imputed based on selected covariates, including the same outcome at the earlier time points, with a random component based on model error using the 'mi impute' command in Stata. The treatment of skewness and correlation in cost and/or outcome data will be investigated using Bayesian and frequentist statistical techniques, such as bootstrapping of cost, outcomes in pairs, or Bayesian bivariate models, and regression approaches, respectively.[17]

Limitations: This document describes a methodology for PIECEs RCT's economic evaluation component. It excludes procedures for gathering data, cleaning data, imputed data, handling missing and censored data, and developing a statistical analysis plan for the PIECEs RCT.

References

[1] Bird J V. Improving outcomes for people with psychosis in Pakistan and India – enhancing the Effectiveness of Community-based care (PIECEs). Protocol. Queen Marry University of London 2017.

[2] Improving community-based mental health care in India and Pakistan https://piecesresearch.com

[3] Bird VJ, Sajun SZ, Peppl R, Evans-Lacko S, Priebe S, Singh S, Venkatraman L, Ramachandran P, Pasha A, Malik A, Qureshi O. Assessing the effectiveness and cost-effectiveness of a solution-focused resource-orientated approach (DIALOG+) to improving the quality of life for people with psychosis in India and Pakistan—a cluster RCT. *Trials*. 2023 Dec;24(1):1-4.

[4] Priebe S, Kelley L, Golden E, McCrone P, Kingdon D, Rutterford C, McCabe R. Effectiveness of structured patient-clinician communication with a solution focused approach (DIALOG+) in community treatment of patients with psychosis–a cluster randomised controlled trial. *BMC psychiatry*. 2013 Dec;13:1-7.

[5] Drummond, M. F., Sculpher, M. J., Claxton, K., Stoddart, G. L., & Torrance, G. W. (2015). Methods for the economic evaluation of health care programmes. Oxford university press.

[6] Priebe S, Kelley L, Golden E, McCrone P, Kingdon D, Rutterford C, McCabe R. Effectiveness of structured patient-clinician communication with a solution focused approach (DIALOG+) in community treatment of patients with psychosis–a cluster randomised controlled trial. *BMC psychiatry*. 2013 Dec;13:1-7.

[7] Drummond M, Manca A, Sculpher M. Increasing the generalizability of economic evaluations: recommendations for the design, analysis, and reporting of studies. *International journal of technology assessment in health care*. 2005 Apr;21(2):165-71.

[8] Thatte U, Hussain S, de Rosas-Valera M, Malik MA. Evidence-based decision on medical technologies in Asia Pacific: experiences from India, Malaysia, Philippines, and Pakistan. *Value in Health.* 2009 Nov 1;12:S18-25.

[9] Chattopadhyay A, Ghosh R, Maji S, Ray TG, Lahiri SK. A time motion study in the immunization clinic of a tertiary care hospital of Kolkata, West Bengal. Indian Journal of Community Medicine: Official Publication of Indian Association of Preventive & Social Medicine. 2012 Jan;37(1):30.

[10] Herdman M, Gudex C, Lloyd A, Janssen MF, Kind P, Parkin D, Bonsel G, Badia X. Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L). Quality of life research. 2011 Dec;20:1727-36.

[11] Husereau D, Drummond M, Augustovski F, de Bekker-Grob E, Briggs AH, Carswell C, Caulley L, Chaiyakunapruk N, Greenberg D, Loder E, Mauskopf J. Consolidated Health Economic Evaluation Reporting Standards (CHEERS) 2022 explanation and elaboration: a report of the ISPOR CHEERS II good practices task force. Value in health. 2022 Jan 1;25(1):10-31.

[12] Malik M, Gu NY, Hussain A, Roudijk B, Purba FD. The EQ-5D-3L Valuation Study in Pakistan. PharmacoEconomics-Open. 2023 Sep 13:1-2.

[13] Van Hout B, Janssen MF, Feng YS, Kohlmann T, Busschbach J, Golicki D, Lloyd A, Scalone L, Kind P, Pickard AS. Interim scoring for the EQ-5D-5L: mapping the EQ-5D-5L to EQ-5D-3L value sets. Value in health. 2012 Jul 1;15(5):708-15.

[14] Manca A, Rice N, Sculpher MJ, Briggs AH. Assessing generalisability by location in trial-based cost-effectiveness analysis: the use of multilevel models. *Health Economics*. 2005 May;14(5):471-85.

[15] Ramsey, S., Willke, R., Briggs, A., Brown, R., Buxton, M., Chawla, A., ... & Reed, S. (2005). Good research practices for cost-effectiveness analysis alongside clinical trials: the ISPOR RCT-CEA task force report. *Value in health*, 8(5), 521-533.

[16] Bird J V. Statistical Analysis plan for Randomized Control Trial in Improving outcomes for people with psychosis in Pakistan and India – enhancing the Effectiveness of Community-based care (PIECEs). Protocol. Queen Marry University of London 2023

[17] Curtis LA, Burns A. Unit costs of health and social care 2015. Personal Social Services Research Unit; 2015.