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Improving psychosocial distress for young adolescents in rural schools of Pakistan: Study protocol of a cluster Randomized Controlled Trial

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Complete List of Authors:	<p>Hamdani, Syed Usman; Shifa Tameer-e-Millat University, Global Institute of Human Development; University of Liverpool Faculty of Health and Life Sciences, Department of Primary Care and Mental Health Huma, Zill-e-; University of Liverpool Faculty of Health and Life Sciences, Department of Primary Care and Mental Health ; University of Liverpool Faculty of Health and Life Sciences, Department of Primary Care and Mental Health Malik, Aiysha; World Health Organization, Mental Health and Substance Use Nizami, Asad; Institute of Psychiatry Baneen, Um ul; Human Development Research Foundation, Child and Adolescent Mental Health; Shifa Tameer-e-Millat University, Global Institute of Human Development Suleman, Nadia; Human Development Research Foundation, Child and Adolescent Mental Health; Shifa Tameer-e-Millat University, Global Institute of Human Development Javed, Hashim; Human Development Research Foundation, Child and Adolescent Mental Health; Shifa Tameer-e-Millat University, Global Institute of Human Development Wang, Duolao; Liverpool School of Tropical Medicine, Department of Clinical Sciences Van Ommeren, Mark; World Health Organization, Dep Mental Health and Substance Use Mazhar, Samra; Pakistan Ministry of National Health Services Regulations and Coordination Khan, Shahzad; World Health Organization Minhas, Fareed; Institue of Psychiatry, Rawalpindi; Shifa Tameer-e-Millat University, Global Institute of Human Development Rahman, Atif; University of Liverpool Faculty of Health and Life Sciences, Primary Care and Mental Health</p>
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Improving psychosocial distress for young adolescents in rural schools of Pakistan: Study protocol of a cluster Randomized Controlled Trial

Syed Usman Hamdani^{1,2,3,5}, Zill-e-Huma^{1,2,3}, Aiysha Malik⁴, Asad Tamizuddin-Nizami⁵,
Um-ul-Baneen^{1,3}, Nadia Suleman^{1,3}, Hashim Javed^{1,3}, Duolao Wang⁶, Mark van
Ommeren⁴, Samra Mazhar⁷, Shahzad Alam Khan⁸, Fareed Aslam Minhas³, Atif Rahman²

Affiliations:

¹Human Development Research Foundation (HDRF), Pakistan

²Department of Primary Care and Mental Health, University of Liverpool, UK

³Global Institute of Human Development, Shifa Tameer-e-Millat University, Pakistan

⁴Department of Mental Health and Substance Use, World Health Organization (WHO),
Geneva, Switzerland

⁵Institute of Psychiatry, Rawalpindi Medical University, Benazir Bhutto Hospital,
Rawalpindi, Pakistan

⁶Global Health Trials Unit, Liverpool School of Tropical Medicine, Liverpool, UK

⁷Ministry of National Health Services, Regulations and Coordination, Pakistan

⁸World Health Organization (WHO), Pakistan Office

Corresponding Author:

Syed Usman Hamdani

Global Institute of Human Development, Shifa Tameer-e-Millat, University, Islamabad,
Pakistan

Email: syedusmanhamdani@gmail.com

Abstract

Introduction: Emotional problems are leading contributors to health burden among adolescents worldwide. There is an urgent need for evidence-based psychological interventions for young people. The present study aims to evaluate the effectiveness of a school-based, group psychological intervention (Early Adolescent Skills for Emotions [EASE]) developed by the World Health Organization (WHO) to improve psychosocial distress in Pakistani adolescents.

Method and analysis: A two-arm, single-blinded, cluster Randomized Controlled Trial (cRCT), with a wait-list control arm is being conducted in school settings of rural Pakistan. Forty eligible public-school clusters have been randomized (stratified by gender) on a 1:1 allocation ratio into intervention (n=20) and control arm (n=20). Following informed consent, 564 adolescents with psychosocial distress (Youth-reported Pediatric Symptoms Checklist [PSC], cut-off ≥ 28) from 40 schools have been enrolled into the trial (14 ± 3 average cluster size) between 2nd to 30th November, 2021. Participants in the intervention arm will receive EASE in 7-weekly adolescents and 3-biweekly caregivers group sessions in schools. The adolescent sessions involve the components of psycho-education, stress management, behavioral activation, problem solving, and relapse prevention. Caregivers will receive training to learn and implement active listening; spending quality time and using praise as a strategy to help their children. The primary outcome is reduction in psychosocial distress at 3-months post-intervention. Secondary outcomes include symptoms of depression and anxiety, caregiver-adolescent relationship and caregivers' wellbeing. Outcomes will be assessed at baseline, immediate 1-week and 3-months-post-intervention. Qualitative process evaluation will explore barriers and facilitators to program implementation in low resource school settings.

Ethics: Ethics approval has been obtained from Central Ethics Committee of University of Liverpool, UK and Ethics Review Committee of WHO Geneva.

Dissemination: If the current study demonstrates effectiveness of the intervention, it will be disseminated by WHO and through peer-reviewed publications.

Trial registration number: ISRCTN17755448

Keywords: adolescents, psychosocial distress, public schools, Early Adolescents Skills for Emotions, non-specialist providers

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3 73 **Strengths and limitations of this study**

- 4 74 - To help young adolescents with internalizing problems, a trans-diagnostic psychological
5 75 intervention was developed by WHO called “Early Adolescent Skills for Emotions (EASE)”.
6 76 The intervention is designed to be delivered through non-specialist facilitators in low resource
7 77 settings.
8 78 - A two arm, single blinded, cluster Randomized Controlled Trial (cRCT), with a wait-list
9 79 control arm, adequate sample size and power and an embedded qualitative process evaluation
10 80 is being conducted to evaluate the effectiveness and cost-effectiveness of EASE in school
11 81 settings of Pakistan.
12 82 - The study is being conducted in one rural geographical area of Pakistan and may need more
13 83 studies in other areas for generalizability.
14 84 - The study uses used self-reported measures for most outcomes. However, these are considered
15 85 standard and used widely in the field.
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87 **List of Abbreviations**

WHO	World Health Organization
EASE	Early Adolescent Skills for Emotions
cRCT	cluster Randomized Controlled Trial
PSC	Paediatric Symptom Checklist
PHQ-A	Patient Health Questionnaire for Adolescents
IDIs	In-Depth Interviews
FGDs	Focus Group Discussions
LMICs	Low and Middle-Income Countries
PM+	Problem Management Plus
PTSD	Post-Traumatic Stress Disorder
IoP-WCC	Institute of Psychiatry-WHO Collaborating Centre for mental health research and training
HDRF	Human Development Research Foundation.
CBT	Cognitive Behavioural Therapy
ENACT	ENhancing Assessment of Common Therapeutic factors
RCADS	Revised Children's Anxiety and Depression Scale
SWEWS	Short Warwick Edinburgh Mental Wellbeing Scale
PedsQL	Paediatric Quality of life
PaedS	Paediatric Self-Stigmatization Scale
CSRI	Client Service Receipt Inventory
PSYCHLOPS	Psychological Outcome Profiles
ODK	Open Data Kit
CSV	Comma Separated Values
AT	Assessment Team
GCP	Good Clinical Practice
CONSORT	Consolidated Standards of Reporting Trials
SD	Standard Deviation

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3	IQR	Inter Quartile Range
4		
5	TSC	Trial Steering Committee
6		
7	mhGAP	Mental Health Gap Action Programme
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9	UoL	University of Liverpool
10		
11	NIHR	National Institutes of Health Research
12		
13	DFID	Department for International Development
14		
15	MRC	Medical Research Council
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89 Introduction

90 Schools are an important public health platform to promote positive youth mental health globally
91 (1, 2). Schools are uniquely placed to reach significant numbers of young people to address their
92 mental health needs, especially in low- and middle-income countries (LMICs), where a lack of
93 child and adolescent mental health services and experts; lack of access to mental health services;
94 low awareness of mental health, and economic and societal barriers such as stigma remain key
95 challenges to the provision of evidence-based mental health services (3). There is growing
96 evidence from both high income and LMICs that school-based mental health programs are
97 associated with beneficial mental health outcomes in adolescents (1). However, scale-up and
98 sustainable implementation of mental health programs for young people in LMICs demands
99 political will, stakeholder involvement, intersectoral coordination and leadership often between
100 health and education sectors (4), particularly in a post-COVID context, where 91% of the world's
101 student population has been negatively impacted by closures of schools due to COVID-19
102 pandemic (5).

103 Rates of anxiety and depression in young people have been exacerbated during COVID-19
104 pandemic (6). Moreover, due to exacerbation of psychosocial stressors including alteration in daily
105 routine and social interactions during COVID-19 pandemic, at-risk adolescents are more likely to
106 develop severe psychological problems. This situation demands an urgent need to provide more
107 effective mental health support to school going adolescents to ensure that young people with
108 symptoms of distress have access to the support that they need in their schools.

109 Youth in Pakistan account for 35% of its population (below the age of 14 years) and are exposed
110 to a number of chronic adversities such as poverty, violence and socio and economic inequalities
111 which makes them more susceptible to develop mental health problems early in their adolescence
112 (7). In addition, the on-going COVID-19 pandemic situation is adversely affecting the economic,
113 social and emotional wellbeing of the population at large and is particularly negatively impacting
114 the wellbeing of adolescents due to nationwide lockdowns, closure of schools and disruption of
115 academic year (8). A recent epidemiological study, conducted pre-COVID-19, with 5,856
116 adolescents from 41 public schools in rural Pakistan reported 25% prevalence rate of psychosocial
117 distress in school going adolescents (9).

118 Recognizing the ever-growing burden of adolescent mental health problems in Pakistan, the
119 Ministry of Health in Pakistan has launched the President's program to promote youth mental
120 health through schools (10). It emphasizes the role of early-life interventions to promote mental
121 health and prevent mental illnesses and takes a multi-tiered approach and recommends training
122 non-specialists such as 'university graduates' to promote socio-emotional wellbeing of school-
123 going adolescents. Under the ambit of President' Program, Early Adolescents Skills for Emotions
124 (EASE) (*strategy 4 of the HAT toolkit*), is being implemented in public schools of rural Pakistan
125 to address internalizing problems in school-going adolescents. EASE was developed by WHO as
126 a brief, trans-diagnostic group psychological intervention designed to be delivered by non-
127 specialists, to help young people aged approximately 10 to 14 years experiencing internalising
128 problems such as psychosocial distress and symptoms of depression and anxiety (11) (*for more
129 details on intervention please see section on interventions below*). EASE has been previously
130 translated in Urdu (*National Language of Pakistan*), culturally adapted for implementation in
131 public schools and feasibility tested in 8 public schools of rural Pakistan using a feasibility cluster
132 randomized controlled trial design ([trial registration NCT04254393](https://clinicaltrials.gov/ct2/show/study/NCT04254393)). The results of the evaluation
133 demonstrated the acceptability and feasibility of the adapted intervention to be delivered by non-

134 specialist facilitators in public school settings of Pakistan and exhibited promising effects on
135 improving adolescent's wellbeing (*publication forthcoming*).

136 The current study aims to evaluate the effectiveness and cost-effectiveness of the culturally
137 adapted EASE intervention compared to wait-list control to improve psychosocial distress in
138 adolescents and improve caregiver-adolescent relationship and caregivers' wellbeing at 3-months
139 post-intervention in public school settings of Pakistan.

140 **Hypotheses**

141 Our primary hypothesis is that *EASE* will be superior compared to *waitlist control*, in reducing the
142 psychosocial distress in adolescents (aged 13-15 years), measured with the self-rated Paediatric
143 Symptom Checklist at 3-months' post-intervention. Our secondary hypotheses are that *EASE* will
144 result in improving adolescent wellbeing, quality of life, problem solving skills, perceived
145 emotional support, caregiver-adolescents relationship and caregivers' wellbeing and reducing
146 somatic complaints and anxiety and depressive symptoms in adolescents.

147 **Methods and analysis**

148 **Study design**

149 A two arm, single blind, cluster Randomized Controlled Trial (cRCT), with a wait-list control arm
150 and an embedded qualitative study is being conducted in public schools of rural sub-district of
151 Gujar Khan in Rawalpindi, Pakistan. The unit of randomization is a school. In the present study,
152 40 eligible school clusters, stratified by gender, have been randomized into intervention and control
153 arms with a 1:1 allocation ratio. Outcomes will be assessed at baseline and post-intervention (1
154 week) and 3-months post-intervention.

155 **Patient and public involvement**

156 The research team has culturally adapted and feasibility tested the intervention by working
157 collaboratively with the adolescents, caregivers and school administration from the same study
158 sub-district. As a part of the formative phase we conducted a) qualitative needs assessments with
159 school adolescents to identify the priority adolescent mental health problems; b) end-user testing
160 workshops with adolescents in school settings to culturally adapt the EASE intervention and c)
161 consultative workshops with relevant stakeholders from Ministries of education and health of
162 Pakistan, school staff including head teachers, teachers, and mental health experts, parents and
163 adolescents to develop a hypothesised pathway for the implementation of school based mental
164 health programs in low resource settings of Pakistan (12). Once the current trial is complete, the
165 findings will be disseminated to participants, ministries of health and education, school education
166 department and wider public through presentations at community and public forums.

167 **Study settings**

168 The study will be conducted in 40 middle and high public schools of rural sub-district of Gujar
169 Khan, located in the Rawalpindi district in the province of Punjab in Pakistan (approx. population
170 of 1000 000). It is a pilot site for the implementation of President's Mental Health Program and
171 falls under the catchment area of Institute of Psychiatry (IoP), Benazir Bhutto Hospital, Rawalpindi
172 which is the sponsoring institute of the present study. The sub-district is semi-rural, with agrarian-
173 based economy and represents typical rural area in the country. The population speaks Punjabi
174 with Potohari being the predominant dialect. In Gujar Khan sub-district, there are 497 public
175 schools (323-primary, 89 middle and 85 high schools). There are 231 schools for boys and 266
176 schools for girls in Gujar Khan in total. The primary decision body for public schools in Gujar
177 Khan is District Education Department and with its permission 40 public schools (20 boys and 20
178 girls schools) were included in the current study. Literacy rates in the study district are 80% (13).

179 Mental health services in Pakistan are provided through specialist mental health units at tertiary
180 healthcare facilities, concentrated in urban centres with little or no mental health care for rural
181 populations. School health services in public schools are provided through School Health and
182 Nutrition Supervisors, who are based at Primary Health Care (PHC) centres and visit schools once
183 a month to screen students for Eye, ENT, Dental, Skin and General Physical problems and if any
184 health problems are identified, the students are referred to the medical officer of the concerned
185 PHC centres.

186 **Research participants**

187 The age range of adolescents in school studying in academic grades 8-10 are 13-15 years of age.
188 Our formative work indicated that challenges faced by adolescents in grades 8-10 include
189 academic stress, expectations of high academic achievements from parents and teachers, peer
190 pressure, interpersonal problems, worries about the future, and stressful home environment
191 (publication forthcoming). These stressors often lead to mental health problems including distress,
192 anxiety and depression like symptoms among adolescents. The need for focused psychological
193 support for the mental health of adolescents in this age group has been identified as a priority by
194 the education sector stakeholders.

195 The research participants for the current study are adolescents, screened positive for psychosocial
196 distress with cut off score of ≥ 28 on self-rated Paediatric Symptoms Checklist (PSC) (validated
197 cut-off score for school going adolescents in Pakistan (9).

199 **Eligibility criteria of participants**

200 **Inclusion criteria**

- 201 • Adolescents aged 13-15 years
- 202 • Living with parents/primary caregivers, attending public middle and high schools in the
203 Gujar Khan sub-district of Rawalpindi, Pakistan.
- 204 • Written parent/primary caregiver informed consent or witnessed consent and adolescent
205 assent for participation in the study.
- 206 • Screened positive on self-reported Paediatric Symptom Checklist (PSC) (cut- off score \geq
207 28).
- 208 • Where there is more than one eligible child in a family unit, we will include the youngest
209 eligible child.

210 **Exclusion criteria**

- 211 • Adolescents at high risk of imminent suicide as reported by the students themselves, or
212 parents/primary caregivers, or identified by the trained assessment team during screening.
- 213 • Adolescents with acute medical conditions who require immediate or on-going in-patient
214 medical or psychiatric care, as reported by student themselves or parents/primary
215 caregivers or identified by the trained assessment team during screening.
- 216 • Adolescents with deafness, blindness and speech difficulties or with a severe mental,
217 neurological or substance use disorders (e.g., psychosis, mutism, intellectual disability,
218 autism, or drug dependence) identified by the trained assessment team during screening.

220 **Sample Size calculations**

221 The cluster unit of randomization has been defined at the school level, stratified by gender. Based
222 on other school- and community-based mental health interventions using the measures assessing

223 psychosocial problems in children (14, 15), we assume an effect size of 0.4 at 3 months' post-
224 intervention follow-up, with 80% power, 0.05 significance, an ICC of 0.05, and a two-sided
225 hypothesis test with 40 school clusters randomised with a 1:1 allocation ratio, stratified by gender
226 and accounting for 20% attrition. This results in a total of 550 adolescents (i.e., 225 in each arm)
227 and about 14 adolescents from each school. Each high school has about 150 adolescents in grade
228 8 and 9, which is more than sufficient to meet our sample size requirement. Stratification by gender
229 will minimize imbalance between groups by factors likely to be associated with our outcome and
230 reduce the between-cluster variability, hence increasing the power of the study.

231 **Recruitment Procedure**

232 The participants were recruited between Nov 2nd and Nov 30th, 2021. Informed consent from head-
233 teachers, parents and assent from children was sought by trained research team for their
234 participation in screening for the research study and for participation into the enrolment of the
235 research study. Since the current study is school-based, the permission to conduct the study was
236 obtained from the school education department. Following informed consents and assents forms
237 for the screening phase, the self-rated Paediatric Symptoms Checklist (PSC) was administered by
238 the trained assessment team to screen adolescents for psychosocial distress in a private location in
239 school settings for maintaining confidentiality. Participants meeting the eligibility criteria were
240 enrolled for the study.

241 **Intervention**

242 **Early Adolescent Skills for Emotions (EASE) Intervention**

243 Developed by the WHO, EASE is a brief, group psychological intervention program (11) based
244 on evidence-informed techniques that are empirically supported for young adolescents living with
245 symptoms of internalising disorders (16). The intervention is comprised of 7 weekly group
246 sessions lasting 90 minutes for the young adolescents and is accompanied by 3 group sessions for
247 their caregivers, each lasting approximately 90 minutes. The young adolescent sessions involve
248 the following empirically supported components: psychoeducation, problem solving, stress
249 management, behavioural activation, and relapse prevention. The caregiver sessions involve
250 psychoeducation, active listening, quality time, praise, caregiver self-care and relapse prevention.
251 The adolescent sessions will be delivered on weekly basis, and the three caregiver sessions are
252 delivered at the third, fifth and seventh weeks of the adolescent intervention. Home practice of the
253 EASE strategies is encouraged between each session for both adolescents and caregivers. Each
254 EASE session is delivered by one primary facilitator and a co-facilitator.

255 **Training and supervision of non-specialist facilitators in 'EASE intervention**

256 EASE delivery school counsellors will be graduates with little or no prior experience of delivering
257 targeted psychological interventions. EASE school counsellors will be selected from these fresh
258 graduate students (having a bachelor degree in Psychology) based upon interviews and successful
259 delivery of practice cases (at least 1 group each) under close supervision.

260 EASE school counsellors will receive 8-days (80-90 hours) of training by the master trainers of
261 the intervention. Intervention training includes education on adversity and its impact upon mental
262 health, basic counselling skills, training in managing distressed participants, delivering EASE,
263 skills in group facilitation, and facilitator self-care. Further, school counsellors will have conducted
264 at least one practice EASE intervention group under close supervision. Only school counsellors
265 assessed as being competent (see quality control below) will be recruited to deliver the EASE
266 intervention in the trial phase.

267 **Supervision**

268 Weekly supervision will be provided to EASE school counsellors by an appropriately qualified
269 and trained supervisor for EASE with a good understanding of the young adolescent project to
270 ensure fidelity of guidance provided, and to support school counsellors; in turn, this supervisor
271 will be supported by clinical supervisors who have been involved in the development or training
272 of EASE on a weekly to fortnightly basis and via Skype. Supervision will involve structured
273 discussion of difficulties encountered in delivering EASE, management of adverse events as well
274 as self-care for the staff. Supervision also forms an integral part of continued training (e.g., through
275 role-plays and associated teaching methods).

276 **Competency and fidelity**

277 Before and after the training of potential EASE providers, competency of the delivery agents will
278 be evaluated using an adapted version of the Enhancing Assessment of Common Therapeutic
279 factors (ENACT) rating scale (17). The ENACT scale is an 18-item assessment for common
280 factors in psychological treatments, including task-sharing initiatives with non-specialists across
281 cultural settings. School counsellors will also record checklists for each session as a measure of
282 self-rated fidelity. An EASE specific checklist and four items assessing facilitation skills will be
283 used to assess treatment fidelity and competency in a random sample of 10-15% of directly
284 observed sessions for each school counsellor.

285 **Wait-list control**

286 The wait-list control participants will receive usual care for the duration of their enrolment in the
287 study. They will receive EASE immediately after trial evaluation on the basis that the results of
288 the study demonstrate positive findings.

289 **Outcome measures**

290 Outcome measures will be administered with the adolescents and their parents at post-intervention
291 and at 3 -months' post-intervention delivery. Assessments will be conducted by the trained
292 assessment team who will be blind to allocation status of the participants. See outcomes measures
293 table 1 given below for the details. All outcome measures have been translated in Urdu and adapted
294 to suit the local cultural context as part of the associated feasibility study (trial registration
295 NCT04254393).

296 **Primary outcome**

297 **Psychosocial distress:** The primary outcome in the present study is change in the scores of
298 adolescent psychosocial distress at 3-month post-intervention. Adolescents' psychosocial distress
299 will be measured at baseline, immediate (1-week), and at 3-months post-intervention delivery in
300 both arms using the Paediatric Symptom Checklist (PSC) (18). The youth version of PSC has 35
301 items and 3 subscales; Externalizing, internalizing and attention problems with cut-offs of 7, 5 and
302 7 respectively. Items are rated on a three-point Likert scale (0= *never*, 1=*sometimes*, 2=*often*).
303 Total score is calculated by summing the responses of all items. The recommended cut-off for
304 administering Paediatric Symptom Checklist for adolescents in a new setting is ≥ 28 (19). The cut-
305 off score of ≥ 28 has been validated in the same study setting previously (9).

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313 **Table 1:** Schedule of assessments

Sr. no.	Outcomes	Timepoints			
		Screening	Baseline	Immediate (1-week) intervention follow-up	(1- post- intervention 3-months post-intervention follow-up)
<i>Primary outcome (child's level)</i>					
1.	PSC	X	X	X	X
<i>Secondary outcomes</i>					
<i>At child's level</i>					
2.	RCADS		X	X	X
3.	Somatic symptoms		X	X	X
4.	SPSI-R		X	X	X
5.	PESS		X	X	X
6.	PHQ-9		X	X	X
7.	SWEMWS		X	X	X
8.	PedsQL		X	X	X
9.	PaedS		X	X	X
10.	PSYCHLOPS-Kid		X	X	X
<i>At caregiver's level</i>					
11.	PedsQL-Family Impact		X	X	X
12.	CSRI		X		X
<i>At both child and caregivers' levels</i>					
13.	APS		X	X	X
14.	SUQ		X	X	X

314 PSC, Paediatric Symptoms Checklist; RCADS, Revised Children's Anxiety and Depression Scale; SPSI-R, Social
 315 Problem-Solving Inventory - Revised Short Form; PESS, Perceived Emotional/Personal Support Scale; PHQ-9,
 316 Patient Health Questionnaire; SWEMWS, Short Warwick Edinburgh Mental Wellbeing Scale; PedsQL, Parent-rated
 317 Paediatric Quality of Life; PaedS, Paediatric Self-Stigmatization Scale; PSYCHLOPS-Kid, Perceived Psychosocial
 318 Profile; CSRI, Client Services Receipt Inventory; APS, Alabama Parenting Scale; SUQ, Strategy Use Questionnaire

319 320 321 **Secondary outcomes**

322 **1. The Revised Children's Anxiety and Depression Scale (RCADS)**

323 The Revised Children's Anxiety and Depression Scale-25 (RCADS-25) (20) is a 25-item scale
 324 that measures levels of anxiety and low mood. The scale has two subscales (Total Anxiety and
 325 Total Depression) and an overall score. All items assess the frequency of symptoms and are rated

326 on a 4-point Likert scale. Each item is scored as 0 (*never*), 1 (*sometimes*), 2 (*often*), or 3 (*always*).
327 Response values for each subscale is summed for calculating raw summary score.

328 **2. Somatic symptoms checklist**

329 The somatic symptoms checklist will be used to measure stress management among adolescents.
330 It consists of 10 items, rated on a 3-point scale (0=*not true*, 1=*somewhat true*, 2=*very true or often*
331 *true*) based on the occurrence of the symptoms. Total score is calculated by summing the responses
332 of all items. Higher score indicates frequent occurrence of somatic symptoms.

333 **2. The Social Problem-Solving Inventory - Revised Short Form (21)** is a self-reporting
334 questionnaire with 25 items. It consists of five subscales with five items each. Two of these
335 subscales, 'positive problem orientation' and 'negative problem orientation', assess functional and
336 dysfunctional cognitive and emotional orientations towards solving problems. The three remaining
337 subscales, 'rational problem solving', 'impulsivity-carelessness style', and 'avoidance style',
338 assess problem-solving skills and behavioural style. The total score of this scale varies between 0
339 and 20 points. Highest scores correspond to better social problem-solving abilities. Social
340 Problem-Solving Inventory – Scale has been used with adolescents in various countries including
341 India and Pakistan (22).

342 **3. The Perceived Emotional/Personal Support Scale (23)** assesses perceived emotional support.
343 Respondents are instructed to list the gender and first initial of three important people in each of
344 three relationship categories: family members, non-family adults, and friends. Using a four-point
345 scale (*hardly at all* to *very much*), respondents answer the following questions about each person
346 listed: "How much do you talk to them about personal concerns?" "How close do you feel to them?"
347 and "How satisfied are you with the help and support they give you?" How much do they talk to
348 you about their concerns? Three support variables are created by averaging all ratings for all
349 persons listed within each relationship category: perceived support from family, non-family adults,
350 and peers. Scores range from 1 to 4.

351 **4. Patient Health Questionnaire (PHQ-9)**

352 PHQ-9, adapted for adolescents (24) will be used to assess depressive symptoms and severity
353 among adolescents. Items are rated on a 4-point Likert scale with 0= *not at all*, 1= *several day*,
354 2= *more than half the days*, 3= *nearly every day*. Total score is calculated by summing the
355 responses of all items. Higher score indicates higher incidence of depressive symptoms. PHQ-9
356 total score for the nine items ranges from 0 to 27.

357 **5. Short Warwick Edinburgh Mental Wellbeing Scale (SWEMWBS)**

358 SWEMWBS (25) is a brief questionnaire designed to measure mental wellbeing of children and
359 adolescents over the past two weeks. It consists of 7 items rated on 'none of the time' to 'all of the
360 time'. The SWEMWBS is scored by first summing the score for each of the seven items and then
361 transforming the total raw scores to metric scores using the SWEMWBS conversion table. The
362 scores range from 7 to 35 and higher scores indicate higher positive mental well-being (26).

363 **6. Parent-rated Paediatric Quality of Life (PedsQL)**

364 Parent-rated Paediatric Quality of Life (PedsQL) (27) will be used to measure child's health related
365 quality of life during the past month. The scale measures child's quality of health on four subscales
366 namely, physical functioning, emotional functioning, social functioning and school functioning.
367 The items are rated on 4 points Likert scale ranging from (1) 'no problem' to (4) 'almost always a
368 problem'. Items are then reverse-scored and linearly transformed to a 0–100, so that higher scores
369 indicate better quality of life. This tool yields a total score (of all 23 items) and domain scores

370 including physical health summary score (8 items), psychosocial health summary score (10 items)
371 and school functioning score (5 items).

372 **7. Paediatric Self-Stigmatization Scale (PaedS)**

373 The PaedS, is a scale developed for measuring stigma in children and adolescents (28). It consists
374 of 4 subscales that measure societal devaluation, personal rejection, self-stigma and secrecy of
375 receiving mental health treatment. The personal rejection subscale (5 items) of the PaedS will be
376 used in the current study. The items are rated on 4-point Likert scale, where higher scores indicate
377 greater stigmatization. The tool has been validated for the content and previously used in Pakistan
378 (29).

379 **8. Paediatric Quality of Life (Peds-QL)-Family impact module**

380 Peds-QL family impact module (30) will be used to assess parents' health related quality of life.
381 PedsQL family impact module is a 36-item scale that measures quality of life on 6 sub-scales
382 namely; physical functioning, emotional functioning, social functioning, cognitive functioning,
383 communication, worry, daily activities and family relationships. Items are rated on a 5-point Likert
384 scale (0 = *never* to 4 = *almost always*). Total score is calculated by summing all 36 items divided
385 by the number of items answered. Higher scores indicate better functioning (less negative impact).
386 (27).

387 **9. Alabama Parenting Scale**

388 Alabama parenting scale (31) will be used to measure parenting practices. Alabama parenting scale
389 is a 42-item measure that encompasses five dimensions of parenting that are relevant to the
390 aetiology and treatment of children's' and adolescents' problems: (1) positive involvement with
391 children, (2) supervision and monitoring, (3) use of positive discipline techniques, (4) consistency
392 in the use of such discipline and (5) use of corporal punishment. Items are rated on a 5-point Likert
393 scale (1 = never to 5 = almost always). Total score is calculated by summing all items. (32).

394 **11. Strategy Use Questionnaire (SUQ)** Strategy Use Questionnaire (SUQ) (33) is designed to
395 measure the use of coping strategies (identifying emotions and using relaxation technique,
396 behavioural activation, problem solving at child and understanding child's internalizing problems,
397 using active listening skill, spending quality time with children, punishing child or using unhealthy
398 disciplinary strategies and using relaxation technique at caregivers). Each item is scored on a
399 frequency scale ranging from 0 (*never*) to 4 (*all of the time*). Total score is calculated by summing
400 all items.

401 **11. Health Services Utilization**

402 The cost of health services utilization from the time proceeding assessment will be assessed with
403 the adapted Client Services Receipt Inventory (CSRI) (34). It has been adapted to use for the
404 families of children with psychosocial distress. It measures the utilization of various health and
405 social care services including time and opportunity losses by the families in the care of their child
406 with psychosocial distress.

407 **Child's psycho-social wellbeing and functioning (PSYCHLOPS)-Kids**

408 Child's insight into his/her problems and wellbeing will be measured using the self-administered
409 PSYCHLOPS-Kids (35). The outcome measure assesses three domains, including problems,
410 functioning and well-being. PSYCHLOPS KIDS has three questionnaires forms i.e., pre- therapy,
411 during therapy and post therapy version. The tool is designed to be user friendly and can be used
412 for children as young as 7 years. The tool has been feasibility tested as part of pilot study.

413

414 **Randomization and blinding**

415 The unit of randomization is schools, which will be stratified by gender. 40 middle and high
416 schools nominated by district education authority have been enrolled in the cRCT. Schools will be
417 randomized on 1:1 allocation ratio by independent researcher using computerized software. The
418 40 schools will be randomized into intervention (n=20) and control arm (n=20). 550 adolescents
419 with psychosocial distress will be recruited from all randomized schools (10-14 adolescents from
420 each cluster). Allocation concealment will be ensured by keeping the random assignments in
421 sequentially numbered sealed envelopes. Due to the nature of the intervention, it is not possible to
422 blind parents, adolescents, school counsellors, intervention supervisors, data and trial manager to
423 the treatment allocation status of trial participants. The assessment team and PIs will be blind to
424 the allocation status of school clusters, while the qualitative research team will be un-blind to
425 allocation status of school clusters. To maintain blinding during the trial, intervention and
426 assessment teams will not have any interaction during the trial by being based at separate office
427 locations. The assessment team will also be non-residents of study sub-district, Gujar Khan.
428 Furthermore, participants including parents, school administration, head teachers, and adolescents
429 will each be individually instructed not to disclose to the assessment team which type of training
430 they are receiving prior to the commencement of any assessment. Fidelity of blinding will be
431 measured by having assessors guess the condition of each participant at the end of each assessment.
432 We hypothesize that assessors will only be able to correctly guess the condition of participants at
433 a chance rate of nearly 50% at follow-up assessments, indicating that blinding is maintained. The
434 trial statistician will also be blind to the allocation status when developing the statistical analysis
435 plan and writing the statistical programs. The statistical analysis plan will be validated using
436 dummy randomization codes. The allocation status of research participants will only be disclosed
437 in a trial steering committee meeting after locking of the database on the completion of the trial.
438 In the event of un-blinding, the point of un-blinding will be recorded, the assessment will be halted,
439 and another assessor will be assigned to complete assessments for that cluster.

440 **Safety measures**

441 Throughout the study, participants will have access to mental health experts at the IoP. When
442 necessary, they will be referred to a mental health specialist for further assessment for any
443 identified child protection issues or management of severe psychiatric problems including suicidal
444 behaviour. School staff and students in the public-sector schools are entitled to health care in public
445 dispensaries and hospitals through an existing referral system. Individuals are able to seek
446 specialist services as walk-in patients and through referrals from primary and secondary health
447 care centres. Travel time from the study area to the specialist mental health care facility is about 1
448 hour using public transport. Free of cost ambulance services will be made available in case of a
449 need for referral from primary health care centres to the specialist facility. At the specialist facility
450 waiting times are minimal (1 hour at the most) and services are available free of cost. Adolescents
451 at-risk of social protection issues are provided appropriate care through collaboration between the
452 district education department and department of social welfare. We will have additional safeguards
453 that will strengthen these mechanisms and we will initiate the appropriate referral to these local
454 authorities via the IoP should the need arise for health and protection concerns in participants.

455 The face-to-face contact with the trained school counsellor will ensure that psychological distress
456 is monitored each week, and a measure of distress conducted pre- and post-intervention will be
457 used to supplement this. School counsellors will be well trained to monitor for sudden changes in
458 mood and potential suicidality, including training in how to respond to suicidality with the

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2
3 459 individual. All staff will be trained in following appropriate referral procedures, via the supervisor
4 460 and trial coordinator, should a concern for suicide or child protection concern arise.

6 461 **Adverse events reporting**

7 462 A critical incident register will be maintained during the study to record serious adverse events
8 463 and other adverse events. Recognition and management of all serious adverse events and other
9 464 adverse events will be included in the training of school counsellors and the research staff. This
10 465 will include a series of steps which have to be followed once such an event occurs including their
11 466 detection, classification, reporting requirements and mitigation. Adverse events will be reported
12 467 to trial ethics committees.

14 468 **Data management**

15 469 All quantitative research data including baseline and follow-up outcome assessment from the
16 470 research participants will be collected by trained assessors electronically using tablet computers
17 471 on an android based application named Open Data Kit (ODK). All research data will be remotely
18 472 uploaded as a Comma Separated Values (CSV) file on the main data server running online using
19 473 ODK by Assessment Team (AT) on each day of assessment. The data server will be GCP
20 474 compliant including a date- and time-stamp for original data entry; an audit trail documenting any
21 475 subsequent changes will be maintained. Data will be exported from the web server at the end of
22 476 each day and will be checked for consistency and quality by the data manager. Exported data sets
23 477 will be stored in password protected computer, only accessible by the data manager. Database will
24 478 be backed-up on a daily basis and the back-up data will be stored on secure hard drives that will
25 479 be stored in a secure location. Process monitoring data such as supervision attendance, number of
26 480 supervision meetings conducted and data of number of intervention strategies implemented will
27 481 be collected in paper form, and this will be manually entered and stored as CSV files. All
28 482 quantitative research data will be deidentified.

29 483 The qualitative data will be collected in audio and paper formats and will be stored in locked filing
30 484 cabinets. It will be manually entered for analysis by separating the identifying information such as
31 485 participants' names and school name from the main data. Identifiable data will never be stored on
32 486 portable devices unless those devices are stored in secure physical storage. Appropriate firewalls,
33 487 encryption, and password protection will be used for network-connected devices used to store
34 488 study data. Qualitative data will be recorded on digital recorders with the informed consent of
35 489 participants, and at the end of each day audio files will be transferred to computers and deleted
36 490 from portable devices, and stored in a password protected folders on computers that are backed-
37 491 up daily. The audio files will be destroyed after transcription.

43 492 **Statistical analysis**

44 493 The findings of the trial will be reported following the updated recommendations of the
45 494 CONSORT 2010 statement: extension to cluster randomized trials (36). This will include the flow
46 495 of clusters and research participants through each stage of the trial, including the number eligible,
47 496 randomly assigned, receiving the intended treatment, completing the study protocol and analysed
48 497 for the primary outcome. Initial analyses will compare baseline characteristics of research
49 498 participants across the two study arms; participants who complete follow-up assessments and
50 499 participants who could not complete follow up assessments; and a comparison of the distribution
51 500 of potential confounding factors. The outcome measures will be summarized at baseline and 3-
52 501 month post-intervention follow-up by intervention arm and overall. These will be summarized by
53 502 means (SD), medians (IQR) or numbers and proportions as appropriate (and including age, gender,

503 baseline outcome score), adjusting for cluster. Data will be cleaned and checked for accuracy prior
504 to analysis. The consort flow for the trial is given below (Figure 1).

505 For the analysis of the primary outcome (reduction in PSC psychosocial distress scores from
506 baseline to 3-months' post intervention follow-up), a linear mixed model will be employed with
507 treatment, visit, interaction between treatment and visit as fixed effects, gender and the baseline
508 value of the PSC psychosocial distress score as covariates, subject and cluster (school cluster) as
509 random effects. In addition, adjusted linear mixed model analysis will be performed with the pre-
510 specified covariates (parent/primary caregivers' education) measured at baseline being added into
511 the above linear mixed model, which will be identified and listed in the statistical analysis plan.
512 The crude and adjusted mean differences in the primary outcome together with its 95% confidence
513 intervals between intervention and control at 3-months will be derived from the mixed models. In
514 addition, subgroup analysis of primary endpoint will be performed on the above pre-specified
515 covariates. Analysis of secondary continuous outcomes with single follow-up measurement will
516 be done using a linear mixed model with treatment as fixed effect, gender and the baseline value
517 of the outcome variable as covariates, and cluster (school cluster) as random effect. Analysis of
518 secondary continuous outcomes with repeated follow-up measurement will be performed in a
519 similar fashion as the primary endpoint analysis. The analysis of binary outcomes will use a
520 generalized linear mixed model with treatment as fixed effect, baseline measurement of the
521 outcome variable and gender as covariates, subject and cluster (school cluster) as random effects.
522 The generalized linear mixed model will have a binomial distribution and logit link function, which
523 will generate odds ratios with their 95% confidence intervals of having an event between
524 intervention and control.

525 Primary data analyses will be based on the intention-to-treat principle. The per-protocol analyses
526 will also be performed as supplemental analysis. Descriptive statistics will be produced for
527 outcome variables and also for baseline characteristics of participants by treatment arm and visit.
528 Continuous variables will be summarized using number of observations, mean, median, standard
529 deviation, min and max by treatment arm and visit; categorical variables will be summarized by
530 the number and percentage of research participants with mental health problems by treatment arm
531 and visit. Adjusted analysis and subgroup analysis will be based on covariates at baseline without
532 non-missing values (37). Detailed imputation methods will be described in the statistical analysis
533 plan. All analyses will be detailed in the statistical analysis plan which will be finalized before the
534 un-blinding of the study. No interim analysis of outcomes is planned.

535 We will conduct a cost-effectiveness analysis to evaluate the cost-effectiveness of EASE
536 intervention in improving outcomes. We will calculate service use for each participant using the
537 data from Client Services Receipt Inventory (CSRI) (34). Service utilisation and the out-of-pocket
538 expenditures of the participants (costs for seeing a doctor or other health-care provider, admission
539 to hospital, medicines, tests and extra help at home) will be collected at baseline and 3-months
540 post-intervention. The data collected through the CSRI will be used to calculate service costs and
541 total costs of care for each participant. Unit costs of services itemised in the CSRI – such as cost
542 per outpatient visit – will be based on locally conducted health facility costing exercises.
543 Service cost data will subsequently be linked to primary and secondary study outcomes, in
544 particular internalizing symptoms scores to assess issues around the value or cost-effectiveness of
545 the EASE intervention. In the event that dominance is not shown, i.e., the EASE intervention is
546 more effective but the costs are also more than in the wait-list group, incremental cost-effectiveness
547 ratios will be computed, together with their confidence intervals (using bootstrapping techniques

to overcome the expected skewness of the cost data). Results will be plotted on a cost-effectiveness plane and presented as cost-effectiveness acceptability curves to show the probability of the intervention being cost-effective at a range of willingness-to-pay threshold levels. A sensitivity analysis will be conducted to take account of uncertainty and imprecision in the measurements, including multiple imputation models for missing values.

Qualitative process evaluation

Qualitative methods will be used to assess assumptions underlying the intervention strategy. In-Depth Interviews (IDIs) and Focus Group Discussion (FGDs) will explore key program implementation outcome variables and will cover intervention: acceptability, feasibility, appropriateness (including cultural appropriateness), fidelity, adoption and participants' view about intervention's perceived impact (both negative and positive) and ethics and safety concerns (Proctor, 2009). Following well-established procedures, qualitative interviews will be recorded, transcribed in Urdu and analysed in the original language (translation into English will only take place for the purpose of international reporting). IDIs and FGDs will be conducted at the preferred venue of the respondents, whether at home, at school, or at any other place of convenience where privacy for IDIs / FGDs can be assured.

Sampling: Interviews will be conducted with both adolescents and caregivers in the intervention including completers and drop outs, non-specialist facilitators, supervisory and school staff (teachers and head teachers). Sampling for qualitative interviews will be purposive based upon the knowledge and exposure to EASE for each category of respondent. Sampling for in-depth interviews will continue until theoretical saturation has been reached, anticipated to require 8 – 15 interviews with each category of respondent.

IDIs and FGDs will be conducted by the qualitative research team who will be trained in the key principles of qualitative interviewing. One interviewer will ask the questions and the other will take notes of the interview. Audio recordings will also be taken. All data will be anonymised and no identifying information will be collected during the interview. The interviews will follow a semi-structured interview guide addressing topics relevant to each category of respondents (Table 2).

Table 2: EASE semi structured interview summary guide

Sample	Themes
Non-specialist facilitators (delivery agents in EASE)	Intervention's acceptability, feasibility, appropriateness (including cultural appropriateness), fidelity, adoption, intervention's perceived impact (both negative and positive), ethics and safety concerns
Beneficiaries (adolescents in EASE)	Intervention's acceptability, feasibility, appropriateness (including cultural appropriateness), adoption, intervention's perceived impact (both negative and positive) and safety concerns
Beneficiaries (caregivers in EASE)	Intervention's acceptability, feasibility, appropriateness (including cultural appropriateness), adoption, intervention's perceived impact (both negative and positive) and safety concerns
Supervisory staff	Intervention's acceptability, feasibility, appropriateness (including cultural appropriateness), fidelity, adoption, intervention's perceived impact (both negative and positive), ethics and safety concerns
School staff	Barriers and facilitator of implementing intervention in school settings including perceived impact of intervention (both negative and positive)

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580 Analysis of in-depth interviews will be thematic, aided by application of the framework approach
581 (38), which complements applied research, offers transparency in the analysis process, and has an
582 ability to move from descriptive narrative accounts to conceptual explanations. Analysis will move
583 through phases of familiarisation, generation of codes, and selection of illustrative quotes (39),
584 conducted by multiple members of the qualitative research team. Data from FDGs and IDIs will
585 be triangulated to ensure a comprehensive understanding through convergence or divergence of
586 findings relating to each topic explored in interviews.

587 **Trial management**

588 The Trial Steering Committee (TSC) comprising of Principal Investigator (PI), Co-Investigator
589 (s), trial coordinator, senior researchers and intervention staff who will meet monthly to oversight
590 the study and manage the trial.

591 **Ethics**

592 Ethical approval for the current study was obtained from Central Ethics Committee of University
593 of Liverpool, UK, Ethics Review Committee of World Health Organization (WHO) Geneva and
594 from Human Development Research Foundation Institutional Review Board, Islamabad, Pakistan.
595 Data collection will be proceeded after seeking informed from the primary caregiver and assent
596 from adolescents. All of the team members will be trained to ensure safety and confidentiality of
597 participants throughout the research. An independent Trial Steering Committee (TSC) will be set-
598 up to ensure human subject protection to the highest standards.

599 **Dissemination**

600 The dissemination of intervention will be carried through peer reviewed publications and training
601 to the relevant institutions to inform the Education and Health Ministries of Pakistan, in order to
602 scale-up program to public sector education. In addition to that the results will be disseminated
603 through WHO's media channels (40). The results of this study will be disseminated in Urdu to
604 community key stakeholders (such as participant school head teachers, children and
605 parents/primary caregivers) through reports or community presentations.

606

607 **Acknowledgment**

608 The study sponsor and funders have no role in the study design; collection, management,
609 analysis, and interpretation of data; writing of the report; and the decision to submit the report
610 for publication.

611

612 **Authors' contributions:** AR (Principal Investigator) conceived the study and was involved in
613 developing the research design and supervising all aspects of the study. SUH (Co-Principal
614 Investigator) was involved in conception of the study, developing the research design, study
615 protocol, finalising the study tools, training and day-to-day supervision of the study team in
616 Pakistan and drafted the initial manuscript. DW (Co-Investigator) was responsible for all the
617 statistical aspects of the study including development of the statistical analysis plan. ZeH (trial
618 coordinator) worked with UH to develop the research design, study protocol, finalising the study
619 tools, training and day-to-day supervision of the study team and drafted the manuscript. AM, ATM,
620 UB, NS, HJ, MvO, SM, SAK and FAM contributed to the writing.

621 All authors read and approved the final manuscript.

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6 626

7 627 **Competing interests:** None declared.
8 628

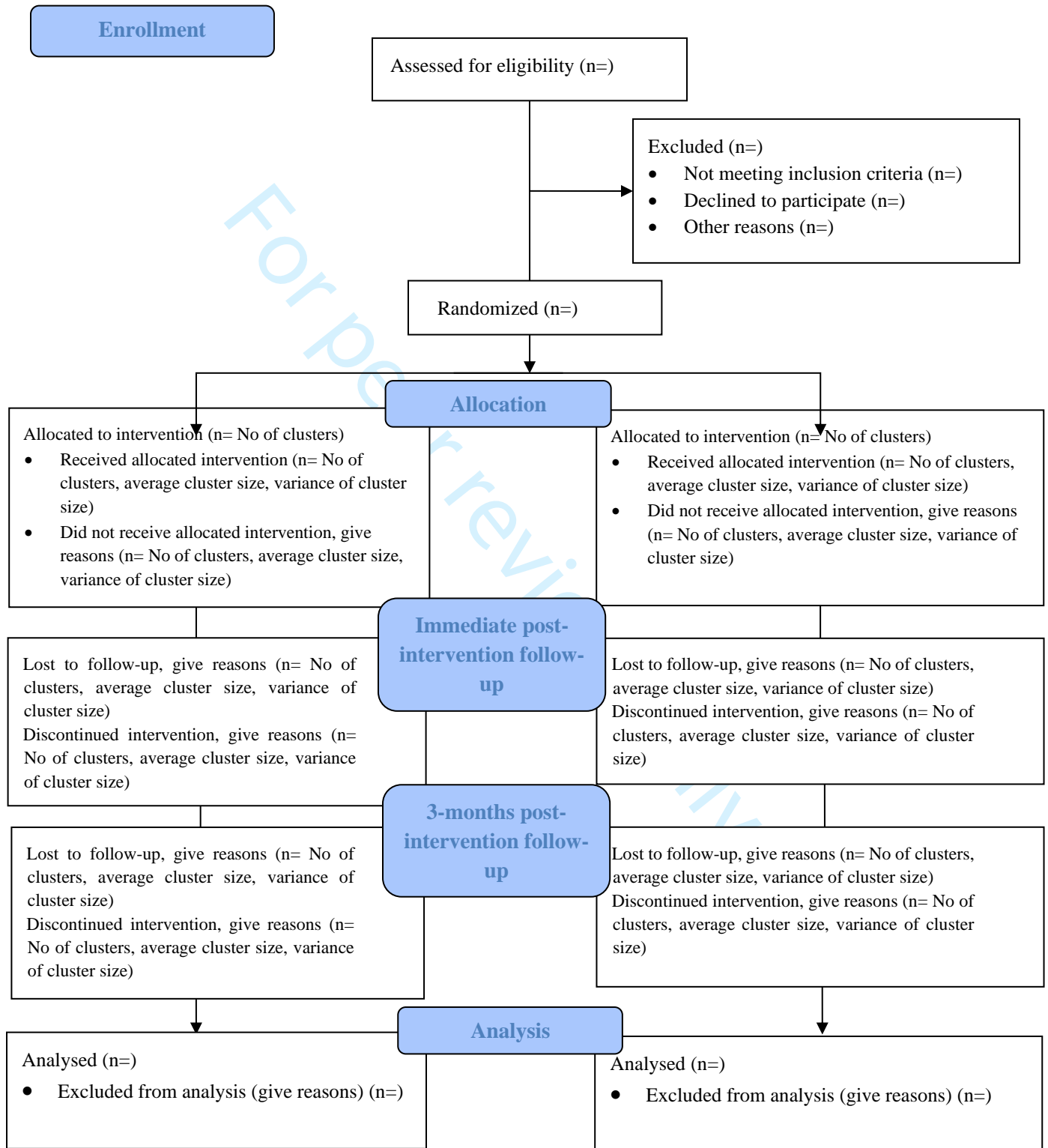
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21 731

Figure 1: Flow of participants through cRCT





STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	Title p.1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	Abstract p. 2
	2b	All items from the World Health Organization Trial Registration Data Set	Included in the registration
Protocol version	3	Date and version identifier	N/A
Funding	4	Sources and types of financial, material, and other support	19
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1 & 18
	5b	Name and contact information for the trial sponsor	N/A
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	18
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	15

1	Introduction			
2				
3	Background and	6a	Description of research question and justification for undertaking the trial, including summary of relevant	6-7
4	rationale		studies (published and unpublished) examining benefits and harms for each intervention	
5				
6		6b	Explanation for choice of comparator	10
7				
8	Objectives	7	Specific objectives or hypotheses	7
9				
10	Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group),	7 & 14
11			allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	
12				
13				
14	Methods: Participants, interventions, and outcomes			
15				
16	Study setting	9	Description of study settings (e.g., community clinic, academic hospital) and list of countries where data will	7&8
17			be collected. Reference to where list of study sites can be obtained	
18				
19	Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and	8
20			individuals who will perform the interventions (eg, surgeons, psychotherapists)	
21				
22	Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be	9-10
23			administered	
24				
25		11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose	N/A
26			change in response to harms, participant request, or improving/worsening disease)	
27				
28		11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence	N/A
29			(eg, drug tablet return, laboratory tests)	
30				
31		11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	10
32				
33	Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood	10-13
34			pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg,	
35			median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen	
36			efficacy and harm outcomes is strongly recommended	
37				
38	Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for	11
39			participants. A schematic diagram is highly recommended (see Figure)	
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1	Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	8-9
2				
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4	Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	9
5				
6				
7	Methods: Assignment of interventions (for controlled trials)			
8	Allocation:			
9				
10	Sequence generation	16a	Method of generating the allocation sequence (e.g., computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	14
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16	Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (e.g., central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	14
17				
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19				
20	Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	14
21				
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23				
24	Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	14
25				
26				
27		17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	14
28				
29				
30				
31	Methods: Data collection, management, and analysis			
32				
33	Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	15&16
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39		18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	N/A
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1	Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	15&16
2				
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5	Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	15-17
6				
7				
8		20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	15-17
9				
10		20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	16-17
11				
12				
13				
14	Methods: Monitoring			
15				
16	Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	18-19
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22		21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	N/A
23				
24				
25	Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	15
26				
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28	Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	N/A
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32	Ethics and dissemination			
33				
34	Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	18
35				
36				
37	Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	N/A
38				
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1	Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	9
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3				
4		26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	N/A
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6				
7	Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	15
8				
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10	Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	19
11				
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13	Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	18
14				
15				
16	Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	N/A
17				
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19				
20	Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, health care professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	18
21				
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24		31b	Authorship eligibility guidelines and any intended use of professional writers	N/A
25				
26		31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	N/A
27				
28				
29	Appendices			
30				
31	Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	N/A
32				
33				
34	Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	N/A
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*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "[Attribution-NonCommercial-NoDerivs 3.0 Unported](https://creativecommons.org/licenses/by/4.0/)" license.

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Improving psychosocial distress for young adolescents in rural schools of Pakistan: Study protocol of a cluster Randomized Controlled Trial

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SCHOLARONE™
Manuscripts

Improving psychosocial distress for young adolescents in rural schools of Pakistan: Study protocol of a cluster Randomized Controlled Trial

Syed Usman Hamdani^{1,2,3,5}, Zill-e-Huma^{1,2,3}, Aiysha Malik⁴, Asad Tamizuddin-Nizami⁵, Um-ul-Baneen^{1,3}, Nadia Suleman^{1,3}, Hashim Javed^{1,3}, Duolao Wang⁶, Mark van Ommeren⁴, Samra Mazhar⁷, Shahzad Alam Khan⁸, Fareed Aslam Minhas³, Atif Rahman²

Affiliations:

¹Human Development Research Foundation (HDRF), Pakistan

²Department of Primary Care and Mental Health, University of Liverpool, UK

³Global Institute of Human Development, Shifa Tameer-e-Millat University, Pakistan

⁴Department of Mental Health and Substance Use, World Health Organization (WHO), Geneva, Switzerland

⁵Institute of Psychiatry, Rawalpindi Medical University, Benazir Bhutto Hospital, Rawalpindi, Pakistan

⁶Global Health Trials Unit, Liverpool School of Tropical Medicine, Liverpool, UK

⁷Ministry of National Health Services, Regulations and Coordination, Pakistan

⁸World Health Organization (WHO), Pakistan Office

Corresponding Author:

Syed Usman Hamdani

Global Institute of Human Development, Shifa Tameer-e-Millat, University, Islamabad, Pakistan

Email: syedusmanhamdani@gmail.com

Abstract

Introduction: Emotional problems are leading contributors to health burden among adolescents worldwide. There is an urgent need for evidence-based psychological interventions for young people. The present study aims to evaluate the effectiveness of a school-based, group psychological intervention (Early Adolescent Skills for Emotions [EASE]) developed by the World Health Organization (WHO) to improve psychosocial distress in Pakistani adolescents.

Method and analysis: A two-arm, single-blinded, cluster Randomized Controlled Trial (cRCT), with a wait-list control arm is being conducted in school settings of rural Pakistan. Forty eligible public-school clusters have been randomized (stratified by gender) on a 1:1 allocation ratio into intervention (n=20) and control arm (n=20). Following informed consent, 564 adolescents with psychosocial distress (Youth-reported Pediatric Symptoms Checklist [PSC], cut-off ≥ 28) from 40 schools have been enrolled into the trial (14 \pm 3 average cluster size) between 2nd to 30th November, 2021. Participants in the intervention arm will receive EASE in 7-weekly adolescents and 3-biweekly caregivers group sessions in schools. The adolescent sessions involve the components of psycho-education, stress management, behavioral activation, problem solving, and relapse prevention. Caregivers will receive training to learn and implement active listening; spending quality time and using praise as a strategy to help their children. The primary outcome is reduction in psychosocial distress at 3-months post-intervention. Secondary outcomes include symptoms of depression and anxiety, caregiver-adolescent relationship and caregivers' wellbeing. Outcomes will be assessed at baseline, immediate 1-week and 3-months-post-intervention. Qualitative process evaluation will explore barriers and facilitators to program implementation in low resource school settings.

Ethics: Ethics approval has been obtained from Central Ethics Committee of University of Liverpool, UK, Ethics Review Committee of WHO Geneva and from the Institutional Review Board of Human Development Research Foundation (HDRF), Pakistan.

Dissemination: The findings of the study will be disseminated by WHO and through peer-reviewed publications.

Trial registration number: ISRCTN17755448

Keywords: adolescents, psychosocial distress, public schools, Early Adolescents Skills for Emotions, non-specialist providers

73

74 Strengths and limitations of this study

- 75 - To help young adolescents with internalizing problems, a trans-diagnostic psychological
76 intervention was developed by WHO called “Early Adolescent Skills for Emotions (EASE)”.
77 The intervention is designed to be delivered through non-specialist facilitators in low resource
78 settings.
- 79 - A two arm, single blinded, cluster Randomized Controlled Trial (cRCT), with a wait-list
80 control arm, adequate sample size and power and an embedded qualitative process evaluation
81 is being conducted to evaluate the effectiveness and cost-effectiveness of EASE in school
82 settings of Pakistan.
- 83 - The study is being conducted in one rural geographical area of Pakistan and may need more
84 studies in other areas for generalizability.
- 85 - The study uses used self-reported measures for most outcomes. However, these are considered
86 standard and used widely in the field.

87

88 **List of Abbreviations**

WHO	World Health Organization
EASE	Early Adolescent Skills for Emotions
cRCT	cluster Randomized Controlled Trial
PSC	Paediatric Symptom Checklist
PHQ-A	Patient Health Questionnaire for Adolescents
IDIs	In-Depth Interviews
FGDs	Focus Group Discussions
LMICs	Low and Middle-Income Countries
PM+	Problem Management Plus
PTSD	Post-Traumatic Stress Disorder
IoP-WCC	Institute of Psychiatry-WHO Collaborating Centre for mental health research and training
HDRF	Human Development Research Foundation.
CBT	Cognitive Behavioural Therapy
ENACT	ENhancing Assessment of Common Therapeutic factors
RCADS	Revised Children's Anxiety and Depression Scale
SWEWS	Short Warwick Edinburgh Mental Wellbeing Scale
PedsQL	Paediatric Quality of life
PaedS	Paediatric Self-Stigmatization Scale
CSRI	Client Service Receipt Inventory
PSYCHLOPS	Psychological Outcome Profiles
ODK	Open Data Kit
CSV	Comma Separated Values
AT	Assessment Team
GCP	Good Clinical Practice
CONSORT	Consolidated Standards of Reporting Trials
SD	Standard Deviation

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3	IQR	Inter Quartile Range
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5	TSC	Trial Steering Committee
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7	mhGAP	Mental Health Gap Action Programme
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9	UoL	University of Liverpool
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11	NIHR	National Institutes of Health Research
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13	DFID	Department for International Development
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15	MRC	Medical Research Council
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For peer review only

90 Introduction

91 Schools are an important public health platform to promote positive youth mental health globally
92 (1, 2). Schools are uniquely placed to reach significant numbers of young people to address their
93 mental health needs, especially in low- and middle-income countries (LMICs), where a lack of
94 child and adolescent mental health services and experts; lack of access to mental health services;
95 low awareness of mental health, and economic and societal barriers such as stigma remain key
96 challenges to the provision of evidence-based mental health services (3). There is growing
97 evidence from both high income and LMICs that school-based mental health programs are
98 associated with beneficial mental health outcomes in adolescents (1). However, scale-up and
99 sustainable implementation of mental health programs for young people in LMICs demands
100 political will, stakeholder involvement, intersectoral coordination and leadership often between
101 health and education sectors (4), particularly in a post-COVID context, where 91% of the world's
102 student population has been negatively impacted by closures of schools due to COVID-19
103 pandemic (5).

104 Rates of anxiety and depression in young people have been exacerbated during COVID-19
105 pandemic (6). Moreover, due to exacerbation of psychosocial stressors including alteration in daily
106 routine and social interactions during COVID-19 pandemic, at-risk adolescents are more likely to
107 develop severe psychological problems. This situation demands an urgent need to provide more
108 effective mental health support to school going adolescents to ensure that young people with
109 symptoms of distress have access to the support that they need in their schools.

110 Youth in Pakistan account for 35% of its population (below the age of 14 years) and are exposed
111 to a number of chronic adversities such as poverty, violence and socio and economic inequalities
112 which makes them more susceptible to develop mental health problems early in their adolescence
113 (7). In addition, the on-going COVID-19 pandemic situation is adversely affecting the economic,
114 social and emotional wellbeing of the population at large and is particularly negatively impacting
115 the wellbeing of adolescents due to nationwide lockdowns, closure of schools and disruption of
116 academic year (8). A recent epidemiological study, conducted pre-COVID-19, with 5,856
117 adolescents from 41 public schools in rural Pakistan reported 25% prevalence rate of psychosocial
118 distress in school going adolescents (9).

119 Recognizing the ever-growing burden of adolescent mental health problems in Pakistan, the
120 Ministry of Health in Pakistan has launched the President's program to promote youth mental
121 health through schools (10). It emphasizes the role of early-life interventions to promote mental
122 health and prevent mental illnesses and takes a multi-tiered approach and recommends training
123 non-specialists such as 'university graduates' to promote socio-emotional wellbeing of school-
124 going adolescents. Under the ambit of President' Program, Early Adolescents Skills for Emotions
125 (EASE) (*strategy 4 of the HAT toolkit*), is being implemented in public schools of rural Pakistan
126 to address internalizing problems in school-going adolescents. EASE was developed by WHO as
127 a brief, trans-diagnostic group psychological intervention designed to be delivered by non-
128 specialists, to help young people aged approximately 10 to 14 years experiencing internalising
129 problems such as psychosocial distress and symptoms of depression and anxiety (11) (*for more
130 details on intervention please see section on interventions below*). EASE has been previously
131 translated in Urdu (*National Language of Pakistan*), culturally adapted for implementation in
132 public schools and feasibility tested in 8 public schools of rural Pakistan using a feasibility cluster
133 randomized controlled trial design ([trial registration NCT04254393](https://clinicaltrials.gov/ct2/show/study/NCT04254393)). The results of the evaluation
134 demonstrated the acceptability and feasibility of the adapted intervention to be delivered by non-

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3 135 specialist facilitators in public school settings of Pakistan and exhibited promising effects on
4 136 improving adolescent's wellbeing (*publication forthcoming*).

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6 137 The current study aims to evaluate the effectiveness and cost-effectiveness of the culturally
7 138 adapted EASE intervention compared to wait-list control to improve psychosocial distress in
8 139 adolescents and improve caregiver-adolescent relationship and caregivers' wellbeing at 3-months
9 140 post-intervention in public school settings of Pakistan.

11 141 **Hypotheses**

12 142 Our primary hypothesis is that *EASE* will be superior compared to *waitlist control*, in reducing the
13 143 psychosocial distress in adolescents (aged 13-15 years), measured with the self-rated Paediatric
14 144 Symptom Checklist at 3-months' post-intervention. Our secondary hypotheses are that *EASE* will
15 145 result in improving adolescent wellbeing, quality of life, problem solving skills, perceived
16 146 emotional support, caregiver-adolescents relationship and caregivers' wellbeing and reducing
17 147 somatic complaints and anxiety and depressive symptoms in adolescents.

19 148 **Methods and analysis**

20 149 **Study design**

21 150 A two arm, single blind, cluster Randomized Controlled Trial (cRCT), with a wait-list control arm
22 151 and an embedded qualitative study is being conducted in public schools of rural sub-district of
23 152 Gujar Khan in Rawalpindi, Pakistan. The unit of randomization is a school. In the present study,
24 153 40 eligible school clusters, stratified by gender, have been randomized into intervention and control
25 154 arms with a 1:1 allocation ratio. Outcomes will be assessed at baseline and post-intervention (1
26 155 week) and 3-months post-intervention.

28 156 **Patient and public involvement**

29 157 The research team has culturally adapted and feasibility tested the intervention by working
30 158 collaboratively with the adolescents, caregivers and school administration from the same study
31 159 sub-district. As a part of the formative phase we conducted a) qualitative needs assessments with
32 160 school adolescents to identify the priority adolescent mental health problems; b) end-user testing
33 161 workshops with adolescents in school settings to culturally adapt the EASE intervention and c)
34 162 consultative workshops with relevant stakeholders from Ministries of education and health of
35 163 Pakistan, school staff including head teachers, teachers, and mental health experts, parents and
36 164 adolescents to develop a hypothesised pathway for the implementation of school based mental
37 165 health programs in low resource settings of Pakistan (12). Once the current trial is complete, the
38 166 findings will be disseminated to participants, ministries of health and education, school education
39 167 department and wider public through presentations at community and public forums.

42 168 **Study settings**

43 169 The study will be conducted in 40 middle and high public schools of rural sub-district of Gujar
44 170 Khan, located in the Rawalpindi district in the province of Punjab in Pakistan (approx. population
45 171 of 1000 000). It is a pilot site for the implementation of President's Mental Health Program and
46 172 falls under the catchment area of Institute of Psychiatry (IoP), Benazir Bhutto Hospital, Rawalpindi
47 173 which is the sponsoring institute of the present study. The sub-district is semi-rural, with agrarian-
48 174 based economy and represents typical rural area in the country. The population speaks Punjabi
49 175 with Potohari being the predominant dialect. In Gujar Khan sub-district, there are 497 public
50 176 schools (323-primary, 89 middle and 85 high schools). There are 231 schools for boys and 266
51 177 schools for girls in Gujar Khan in total. The primary decision body for public schools in Gujar
52 178 Khan is District Education Department and with its permission 40 public schools (20 boys and 20
53 179 girls schools) were included in the current study. Literacy rates in the study district are 80% (13).

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3 180 Mental health services in Pakistan are provided through specialist mental health units at tertiary
4 181 healthcare facilities, concentrated in urban centres with little or no mental health care for rural
5 182 populations. School health services in public schools are provided through School Health and
6 183 Nutrition Supervisors, who are based at Primary Health Care (PHC) centres and visit schools once
7 184 a month to screen students for Eye, ENT, Dental, Skin and General Physical problems and if any
8 185 health problems are identified, the students are referred to the medical officer of the concerned
9 186 PHC centres.

11 187 **Research participants**

12 188 The age range of adolescents in school studying in academic grades 8-10 are 13-15 years of age.
13 189 Our formative work indicated that challenges faced by adolescents in grades 8-10 include
14 190 academic stress, expectations of high academic achievements from parents and teachers, peer
15 191 pressure, interpersonal problems, worries about the future, and stressful home environment
16 192 (publication forthcoming). These stressors often lead to mental health problems including distress,
17 193 anxiety and depression like symptoms among adolescents. The need for focused psychological
18 194 support for the mental health of adolescents in this age group has been identified as a priority by
19 195 the education sector stakeholders.

22 196 The research participants for the current study are adolescents, screened positive for psychosocial
23 197 distress with cut off score of ≥ 28 on self-rated Paediatric Symptoms Checklist (PSC) (validated
24 198 cut-off score for school going adolescents in Pakistan (9).

27 200 **Eligibility criteria of participants**

28 201 **Inclusion criteria**

- 29 202 • Adolescents aged 13-15 years
- 30 203 • Living with parents/primary caregivers, attending public middle and high schools in the
- 31 204 Gujar Khan sub-district of Rawalpindi, Pakistan.
- 32 205 • Written parent/primary caregiver informed consent or witnessed consent and adolescent
- 33 206 assent for participation in the study.
- 34 207 • Screened positive on self-reported Paediatric Symptom Checklist (PSC) (cut- off score \geq
- 35 208 28).
- 36 209 • Where there is more than one eligible child in a family unit, we will include the youngest
- 37 210 eligible child.

41 211 **Exclusion criteria**

- 42 212 • Adolescents at high risk of imminent suicide as reported by the students themselves, or
- 43 213 parents/primary caregivers, or identified by the trained assessment team during screening.
- 44 214 • Adolescents with acute medical conditions who require immediate or on-going in-patient
- 45 215 medical or psychiatric care, as reported by student themselves or parents/primary
- 46 216 caregivers or identified by the trained assessment team during screening.
- 47 217 • Adolescents with deafness, blindness and speech difficulties or with a severe mental,
- 48 218 neurological or substance use disorders (e.g., psychosis, mutism, intellectual disability,
- 49 219 autism, or drug dependence) identified by the trained assessment team during screening.

53 221 **Sample Size calculations**

54 222 The cluster unit of randomization has been defined at the school level, stratified by gender. Based
55 223 on other school- and community-based mental health interventions using the measures assessing

224 psychosocial problems in children (14, 15), we assume an effect size of 0.4 at 3 months' post-
225 intervention follow-up, with 80% power, 0.05 significance, an ICC of 0.05, and a two-sided
226 hypothesis test with 40 school clusters randomised with a 1:1 allocation ratio, stratified by gender
227 and accounting for 20% attrition. This results in a total of 550 adolescents (i.e., 225 in each arm)
228 and about 14 adolescents from each school. Each high school has about 150 adolescents in grade
229 8 and 9, which is more than sufficient to meet our sample size requirement. Stratification by gender
230 will minimize imbalance between groups by factors likely to be associated with our outcome and
231 reduce the between-cluster variability, hence increasing the power of the study.

232 **Recruitment Procedure**

233 The participants were recruited between Nov 2nd and Nov 30th, 2021. Informed consent from head-
234 teachers, parents and assent from children was sought by trained research team for their
235 participation in screening for the research study and for participation into the enrolment of the
236 research study. Since the current study is school-based, the permission to conduct the study was
237 obtained from the school education department. Following informed consents and assents forms
238 for the screening phase, the self-rated Paediatric Symptoms Checklist (PSC) was administered by
239 the trained assessment team to screen adolescents for psychosocial distress in a private location in
240 school settings for maintaining confidentiality. Participants meeting the eligibility criteria were
241 enrolled for the study.

242 **Intervention**

243 **Early Adolescent Skills for Emotions (EASE) Intervention**

244 Developed by the WHO, EASE is a brief, group psychological intervention program (11) based
245 on evidence-informed techniques that are empirically supported for young adolescents living with
246 symptoms of internalising disorders (16). The intervention is comprised of 7 weekly group
247 sessions lasting 90 minutes for the young adolescents and is accompanied by 3 group sessions for
248 their caregivers, each lasting approximately 90 minutes. The young adolescent sessions involve
249 the following empirically supported components: psychoeducation, problem solving, stress
250 management, behavioural activation, and relapse prevention. The caregiver sessions involve
251 psychoeducation, active listening, quality time, praise, caregiver self-care and relapse prevention.
252 The adolescent sessions will be delivered on weekly basis, and the three caregiver sessions are
253 delivered at the third, fifth and seventh weeks of the adolescent intervention. Home practice of the
254 EASE strategies is encouraged between each session for both adolescents and caregivers. Each
255 EASE session is delivered by one primary facilitator and a co-facilitator.

256 **Training and supervision of non-specialist facilitators in 'EASE intervention**

257 EASE delivery school counsellors will be graduates with little or no prior experience of delivering
258 targeted psychological interventions. EASE school counsellors will be selected from these fresh
259 graduate students (having a bachelor degree in Psychology) based upon interviews and successful
260 delivery of practice cases (at least 1 group each) under close supervision.

261 EASE school counsellors will receive 8-days (80-90 hours) of training by the master trainers of
262 the intervention. Intervention training includes education on adversity and its impact upon mental
263 health, basic counselling skills, training in managing distressed participants, delivering EASE,
264 skills in group facilitation, and facilitator self-care. Further, school counsellors will have conducted
265 at least one practice EASE intervention group under close supervision. Only school counsellors
266 assessed as being competent (see quality control below) will be recruited to deliver the EASE
267 intervention in the trial phase.

268 **Supervision**

269 Weekly supervision will be provided to EASE school counsellors by an appropriately qualified
270 and trained supervisor for EASE with a good understanding of the young adolescent project to
271 ensure fidelity of guidance provided, and to support school counsellors; in turn, this supervisor
272 will be supported by clinical supervisors who have been involved in the development or training
273 of EASE on a weekly to fortnightly basis and via Skype. Supervision will involve structured
274 discussion of difficulties encountered in delivering EASE, management of adverse events as well
275 as self-care for the staff. Supervision also forms an integral part of continued training (e.g., through
276 role-plays and associated teaching methods).

277 **Competency and fidelity**

278 Before and after the training of potential EASE providers, competency of the delivery agents will
279 be evaluated using an adapted version of the Enhancing Assessment of Common Therapeutic
280 factors (ENACT) rating scale (17). The ENACT scale is an 18-item assessment for common
281 factors in psychological treatments, including task-sharing initiatives with non-specialists across
282 cultural settings. School counsellors will also record checklists for each session as a measure of
283 self-rated fidelity. An EASE specific checklist and four items assessing facilitation skills will be
284 used to assess treatment fidelity and competency in a random sample of 10-15% of directly
285 observed sessions for each school counsellor.

286 **Wait-list control**

287 The wait-list control participants will receive usual care for the duration of their enrolment in the
288 study. They will receive EASE immediately after trial evaluation on the basis that the results of
289 the study demonstrate positive findings.

290 **Outcome measures**

291 Outcome measures will be administered with the adolescents and their parents at post-intervention
292 and at 3 -months' post-intervention delivery. Assessments will be conducted by the trained
293 assessment team who will be blind to allocation status of the participants. See outcomes measures
294 table 1 given below for the details. All outcome measures have been translated in Urdu and adapted
295 to suit the local cultural context as part of the associated feasibility study (trial registration
296 NCT04254393).

297 **Primary outcome**

298 **Psychosocial distress:** The primary outcome in the present study is change in the scores of
299 adolescent psychosocial distress at 3-month post-intervention. Adolescents' psychosocial distress
300 will be measured at baseline, immediate (1-week), and at 3-months post-intervention delivery in
301 both arms using the Paediatric Symptom Checklist (PSC) (18). The youth version of PSC has 35
302 items and 3 subscales; Externalizing, internalizing and attention problems with cut-offs of 7, 5 and
303 7 respectively. Items are rated on a three-point Likert scale (0= *never*, 1=*sometimes*, 2=*often*).
304 Total score is calculated by summing the responses of all items. The recommended cut-off for
305 administering Paediatric Symptom Checklist for adolescents in a new setting is ≥ 28 (19). The cut-
306 off score of ≥ 28 has been validated in the same study setting previously (9).

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314 **Table 1:** Schedule of assessments

Sr. no.	Outcomes	Timepoints			
		Screening	Baseline	Immediate (1-week) intervention follow-up	(1- post- intervention follow-up
<i>Primary outcome (child's level)</i>					
1.	PSC	X	X	X	X
<i>Secondary outcomes</i>					
<i>At child's level</i>					
2.	RCADS		X	X	X
3.	Somatic symptoms		X	X	X
4.	SPSI-R		X	X	X
5.	PESS		X	X	X
6.	PHQ-9		X	X	X
7.	SWEMWS		X	X	X
8.	PedsQL		X	X	X
9.	PaedS		X	X	X
10.	PSYCHLOPS-Kid		X	X	X
<i>At caregiver's level</i>					
11.	PedsQL-Family Impact		X	X	X
12.	CSRI		X		X
<i>At both child and caregivers' levels</i>					
13.	APS		X	X	X
14.	SUQ		X	X	X

315 PSC, Paediatric Symptoms Checklist; RCADS, Revised Children's Anxiety and Depression Scale; SPSI-R, Social
 316 Problem-Solving Inventory - Revised Short Form; PESS, Perceived Emotional/Personal Support Scale; PHQ-9,
 317 Patient Health Questionnaire; SWEMWS, Short Warwick Edinburgh Mental Wellbeing Scale; PedsQL, Parent-rated
 318 Paediatric Quality of Life; PaedS, Paediatric Self-Stigmatization Scale; PSYCHLOPS-Kid, Perceived Psychosocial
 319 Profile; CSRI, Client Services Receipt Inventory; APS, Alabama Parenting Scale; SUQ, Strategy Use Questionnaire

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322 **Secondary outcomes**323 **1. The Revised Children's Anxiety and Depression Scale (RCADS)**

324 The Revised Children's Anxiety and Depression Scale-25 (RCADS-25) (20) is a 25-item scale
 325 that measures levels of anxiety and low mood. The scale has two subscales (Total Anxiety and
 326 Total Depression) and an overall score. All items assess the frequency of symptoms and are rated

327 on a 4-point Likert scale. Each item is scored as 0 (*never*), 1 (*sometimes*), 2 (*often*), or 3 (*always*).
328 Response values for each subscale is summed for calculating raw summary score.

329 **2. Somatic symptoms checklist**

330 The somatic symptoms checklist will be used to measure stress management among adolescents.
331 It consists of 10 items, rated on a 3-point scale (0=*not true*, 1=*somewhat true*, 2=*very true or often*
332 *true*) based on the occurrence of the symptoms. Total score is calculated by summing the responses
333 of all items. Higher score indicates frequent occurrence of somatic symptoms.

334 **2. The Social Problem-Solving Inventory - Revised Short Form (21)** is a self-reporting
335 questionnaire with 25 items. It consists of five subscales with five items each. Two of these
336 subscales, 'positive problem orientation' and 'negative problem orientation', assess functional and
337 dysfunctional cognitive and emotional orientations towards solving problems. The three remaining
338 subscales, 'rational problem solving', 'impulsivity-carelessness style', and 'avoidance style',
339 assess problem-solving skills and behavioural style. The total score of this scale varies between 0
340 and 20 points. Highest scores correspond to better social problem-solving abilities. Social
341 Problem-Solving Inventory – Scale has been used with adolescents in various countries including
342 India and Pakistan (22).

343 **3. The Perceived Emotional/Personal Support Scale (23)** assesses perceived emotional support.
344 Respondents are instructed to list the gender and first initial of three important people in each of
345 three relationship categories: family members, non-family adults, and friends. Using a four-point
346 scale (*hardly at all to very much*), respondents answer the following questions about each person
347 listed: "How much do you talk to them about personal concerns?" "How close do you feel to them?"
348 and "How satisfied are you with the help and support they give you?" How much do they talk to
349 you about their concerns? Three support variables are created by averaging all ratings for all
350 persons listed within each relationship category: perceived support from family, non-family adults,
351 and peers. Scores range from 1 to 4.

352 **4. Patient Health Questionnaire (PHQ-9)**

353 PHQ-9, adapted for adolescents (24) will be used to assess depressive symptoms and severity
354 among adolescents. Items are rated on a 4-point Likert scale with 0= *not at all*, 1= *several day*,
355 2= *more than half the days*, 3= *nearly every day*. Total score is calculated by summing the
356 responses of all items. Higher score indicates higher incidence of depressive symptoms. PHQ-9
357 total score for the nine items ranges from 0 to 27.

358 **5. Short Warwick Edinburgh Mental Wellbeing Scale (SWEMWBS)**

359 SWEMWBS (25) is a brief questionnaire designed to measure mental wellbeing of children and
360 adolescents over the past two weeks. It consists of 7 items rated on 'none of the time' to 'all of the
361 time'. The SWEMWBS is scored by first summing the score for each of the seven items and then
362 transforming the total raw scores to metric scores using the SWEMWBS conversion table. The
363 scores range from 7 to 35 and higher scores indicate higher positive mental well-being (26).

364 **6. Parent-rated Paediatric Quality of Life (PedsQL)**

365 Parent-rated Paediatric Quality of Life (PedsQL) (27) will be used to measure child's health related
366 quality of life during the past month. The scale measures child's quality of health on four subscales
367 namely, physical functioning, emotional functioning, social functioning and school functioning.
368 The items are rated on 4 points Likert scale ranging from (1) 'no problem' to (4) 'almost always a
369 problem'. Items are then reverse-scored and linearly transformed to a 0–100, so that higher scores
370 indicate better quality of life. This tool yields a total score (of all 23 items) and domain scores

371 including physical health summary score (8 items), psychosocial health summary score (10 items)
372 and school functioning score (5 items).

373 **7. Paediatric Self-Stigmatization Scale (PaedS)**

374 The PaedS, is a scale developed for measuring stigma in children and adolescents (28). It consists
375 of 4 subscales that measure societal devaluation, personal rejection, self-stigma and secrecy of
376 receiving mental health treatment. The personal rejection subscale (5 items) of the PaedS will be
377 used in the current study. The items are rated on 4-point Likert scale, where higher scores indicate
378 greater stigmatization. The tool has been validated for the content and previously used in Pakistan
379 (29).

380 **8. Paediatric Quality of Life (Peds-QL)-Family impact module**

381 Peds-QL family impact module (30) will be used to assess parents' health related quality of life.
382 PedsQL family impact module is a 36-item scale that measures quality of life on 6 sub-scales
383 namely; physical functioning, emotional functioning, social functioning, cognitive functioning,
384 communication, worry, daily activities and family relationships. Items are rated on a 5-point Likert
385 scale (0 = *never* to 4 = *almost always*). Total score is calculated by summing all 36 items divided
386 by the number of items answered. Higher scores indicate better functioning (less negative impact).
387 (27).

388 **9. Alabama Parenting Scale**

389 Alabama parenting scale (31) will be used to measure parenting practices. Alabama parenting scale
390 is a 42-item measure that encompasses five dimensions of parenting that are relevant to the
391 aetiology and treatment of children's' and adolescents' problems: (1) positive involvement with
392 children, (2) supervision and monitoring, (3) use of positive discipline techniques, (4) consistency
393 in the use of such discipline and (5) use of corporal punishment. Items are rated on a 5-point Likert
394 scale (1 = never to 5 = almost always). Total score is calculated by summing all items. (32).

395 **11. Strategy Use Questionnaire (SUQ)** Strategy Use Questionnaire (SUQ) (33) is designed to
396 measure the use of coping strategies (identifying emotions and using relaxation technique,
397 behavioural activation, problem solving at child and understanding child's internalizing problems,
398 using active listening skill, spending quality time with children, punishing child or using unhealthy
399 disciplinary strategies and using relaxation technique at caregivers). Each item is scored on a
400 frequency scale ranging from 0 (*never*) to 4 (*all of the time*). Total score is calculated by summing
401 all items.

402 **11. Health Services Utilization**

403 The cost of health services utilization from the time proceeding assessment will be assessed with
404 the adapted Client Services Receipt Inventory (CSRI) (34). It has been adapted to use for the
405 families of children with psychosocial distress. It measures the utilization of various health and
406 social care services including time and opportunity losses by the families in the care of their child
407 with psychosocial distress.

408 **Child's psycho-social wellbeing and functioning (PSYCHLOPS)-Kids**

409 Child's insight into his/her problems and wellbeing will be measured using the self-administered
410 PSYCHLOPS-Kids (35). The outcome measure assesses three domains, including problems,
411 functioning and well-being. PSYCHLOPS KIDS has three questionnaires forms i.e., pre- therapy,
412 during therapy and post therapy version. The tool is designed to be user friendly and can be used
413 for children as young as 7 years. The tool has been feasibility tested as part of pilot study.

414

415 **Randomization and blinding**

416 The unit of randomization is schools, which will be stratified by gender. 40 middle and high
417 schools nominated by district education authority have been enrolled in the cRCT. Schools will be
418 randomized on 1:1 allocation ratio by independent researcher using computerized software. The
419 40 schools will be randomized into intervention (n=20) and control arm (n=20). 550 adolescents
420 with psychosocial distress will be recruited from all randomized schools (10-14 adolescents from
421 each cluster). Allocation concealment will be ensured by keeping the random assignments in
422 sequentially numbered sealed envelopes. Due to the nature of the intervention, it is not possible to
423 blind parents, adolescents, school counsellors, intervention supervisors, data and trial manager to
424 the treatment allocation status of trial participants. The assessment team and PIs will be blind to
425 the allocation status of school clusters, while the qualitative research team will be un-blind to
426 allocation status of school clusters. To maintain blinding during the trial, intervention and
427 assessment teams will not have any interaction during the trial by being based at separate office
428 locations. The assessment team will also be non-residents of study sub-district, Gujar Khan.
429 Furthermore, participants including parents, school administration, head teachers, and adolescents
430 will each be individually instructed not to disclose to the assessment team which type of training
431 they are receiving prior to the commencement of any assessment. Fidelity of blinding will be
432 measured by having assessors guess the condition of each participant at the end of each assessment.
433 We hypothesize that assessors will only be able to correctly guess the condition of participants at
434 a chance rate of nearly 50% at follow-up assessments, indicating that blinding is maintained. The
435 trial statistician will also be blind to the allocation status when developing the statistical analysis
436 plan and writing the statistical programs. The statistical analysis plan will be validated using
437 dummy randomization codes. The allocation status of research participants will only be disclosed
438 in a trial steering committee meeting after locking of the database on the completion of the trial.
439 In the event of un-blinding, the point of un-blinding will be recorded, the assessment will be halted,
440 and another assessor will be assigned to complete assessments for that cluster.

441 **Safety measures**

442 Throughout the study, participants will have access to mental health experts at the IoP. When
443 necessary, they will be referred to a mental health specialist for further assessment for any
444 identified child protection issues or management of severe psychiatric problems including suicidal
445 behaviour. School staff and students in the public-sector schools are entitled to health care in public
446 dispensaries and hospitals through an existing referral system. Individuals are able to seek
447 specialist services as walk-in patients and through referrals from primary and secondary health
448 care centres. Travel time from the study area to the specialist mental health care facility is about 1
449 hour using public transport. Free of cost ambulance services will be made available in case of a
450 need for referral from primary health care centres to the specialist facility. At the specialist facility
451 waiting times are minimal (1 hour at the most) and services are available free of cost. Adolescents
452 at-risk of social protection issues are provided appropriate care through collaboration between the
453 district education department and department of social welfare. We will have additional safeguards
454 that will strengthen these mechanisms and we will initiate the appropriate referral to these local
455 authorities via the IoP should the need arise for health and protection concerns in participants.

456 The face-to-face contact with the trained school counsellor will ensure that psychological distress
457 is monitored each week, and a measure of distress conducted pre- and post-intervention will be
458 used to supplement this. School counsellors will be well trained to monitor for sudden changes in
459 mood and potential suicidality, including training in how to respond to suicidality with the

individual. All staff will be trained in following appropriate referral procedures, via the supervisor and trial coordinator, should a concern for suicide or child protection concern arise.

Adverse events reporting

A critical incident register will be maintained during the study to record serious adverse events and other adverse events. Recognition and management of all serious adverse events and other adverse events will be included in the training of school counsellors and the research staff. This will include a series of steps which have to be followed once such an event occurs including their detection, classification, reporting requirements and mitigation. Adverse events will be reported to trial ethics committees.

Data management

All quantitative research data including baseline and follow-up outcome assessment from the research participants will be collected by trained assessors electronically using tablet computers on an android based application named Open Data Kit (ODK). All research data will be remotely uploaded as a Comma Separated Values (CSV) file on the main data server running online using ODK by Assessment Team (AT) on each day of assessment. The data server will be GCP compliant including a date- and time-stamp for original data entry; an audit trail documenting any subsequent changes will be maintained. Data will be exported from the web server at the end of each day and will be checked for consistency and quality by the data manager. Exported data sets will be stored in password protected computer, only accessible by the data manager. Database will be backed-up on a daily basis and the back-up data will be stored on secure hard drives that will be stored in a secure location. Process monitoring data such as supervision attendance, number of supervision meetings conducted and data of number of intervention strategies implemented will be collected in paper form, and this will be manually entered and stored as CSV files. All quantitative research data will be deidentified.

The qualitative data will be collected in audio and paper formats and will be stored in locked filing cabinets. It will be manually entered for analysis by separating the identifying information such as participants' names and school name from the main data. Identifiable data will never be stored on portable devices unless those devices are stored in secure physical storage. Appropriate firewalls, encryption, and password protection will be used for network-connected devices used to store study data. Qualitative data will be recorded on digital recorders with the informed consent of participants, and at the end of each day audio files will be transferred to computers and deleted from portable devices, and stored in a password protected folders on computers that are backed-up daily. The audio files will be destroyed after transcription.

Statistical analysis

The findings of the trial will be reported following the updated recommendations of the CONSORT 2010 statement: extension to cluster randomized trials (36). This will include the flow of clusters and research participants through each stage of the trial, including the number eligible, randomly assigned, receiving the intended treatment, completing the study protocol and analysed for the primary outcome. Initial analyses will compare baseline characteristics of research participants across the two study arms; participants who complete follow-up assessments and participants who could not complete follow up assessments; and a comparison of the distribution of potential confounding factors. The outcome measures will be summarized at baseline and 3-month post-intervention follow-up by intervention arm and overall. These will be summarized by means (SD), medians (IQR) or numbers and proportions as appropriate (and including age, gender,

504 baseline outcome score), adjusting for cluster. Data will be cleaned and checked for accuracy prior
505 to analysis. The consort flow for the trial is given below (Figure 1).

506 For the analysis of the primary outcome (reduction in PSC psychosocial distress scores from
507 baseline to 3-months' post intervention follow-up), a linear mixed model will be employed with
508 treatment, visit, interaction between treatment and visit as fixed effects, gender and the baseline
509 value of the PSC psychosocial distress score as covariates, subject and cluster (school cluster) as
510 random effects. In addition, adjusted linear mixed model analysis will be performed with the pre-
511 specified covariates (parent/primary caregivers' education) measured at baseline being added into
512 the above linear mixed model, which will be identified and listed in the statistical analysis plan.
513 The crude and adjusted mean differences in the primary outcome together with its 95% confidence
514 intervals between intervention and control at 3-months will be derived from the mixed models. In
515 addition, subgroup analysis of primary endpoint will be performed on the above pre-specified
516 covariates. Analysis of secondary continuous outcomes with single follow-up measurement will
517 be done using a linear mixed model with treatment as fixed effect, gender and the baseline value
518 of the outcome variable as covariates, and cluster (school cluster) as random effect. Analysis of
519 secondary continuous outcomes with repeated follow-up measurement will be performed in a
520 similar fashion as the primary endpoint analysis. The analysis of binary outcomes will use a
521 generalized linear mixed model with treatment as fixed effect, baseline measurement of the
522 outcome variable and gender as covariates, subject and cluster (school cluster) as random effects.
523 The generalized linear mixed model will have a binomial distribution and logit link function, which
524 will generate odds ratios with their 95% confidence intervals of having an event between
525 intervention and control.

526 Primary data analyses will be based on the intention-to-treat principle. The per-protocol analyses
527 will also be performed as supplemental analysis. Descriptive statistics will be produced for
528 outcome variables and also for baseline characteristics of participants by treatment arm and visit.
529 Continuous variables will be summarized using number of observations, mean, median, standard
530 deviation, min and max by treatment arm and visit; categorical variables will be summarized by
531 the number and percentage of research participants with mental health problems by treatment arm
532 and visit. Adjusted analysis and subgroup analysis will be based on covariates at baseline without
533 non-missing values (37). Detailed imputation methods will be described in the statistical analysis
534 plan. All analyses will be detailed in the statistical analysis plan which will be finalized before the
535 un-blinding of the study. No interim analysis of outcomes is planned.

536 We will conduct a cost-effectiveness analysis to evaluate the cost-effectiveness of EASE
537 intervention in improving outcomes. We will calculate service use for each participant using the
538 data from Client Services Receipt Inventory (CSRI) (34). Service utilisation and the out-of-pocket
539 expenditures of the participants (costs for seeing a doctor or other health-care provider, admission
540 to hospital, medicines, tests and extra help at home) will be collected at baseline and 3-months
541 post-intervention. The data collected through the CSRI will be used to calculate service costs and
542 total costs of care for each participant. Unit costs of services itemised in the CSRI – such as cost
543 per outpatient visit – will be based on locally conducted health facility costing exercises.
544 Service cost data will subsequently be linked to primary and secondary study outcomes, in
545 particular internalizing symptoms scores to assess issues around the value or cost-effectiveness of
546 the EASE intervention. In the event that dominance is not shown, i.e., the EASE intervention is
547 more effective but the costs are also more than in the wait-list group, incremental cost-effectiveness
548 ratios will be computed, together with their confidence intervals (using bootstrapping techniques

549 to overcome the expected skewness of the cost data). Results will be plotted on a cost-effectiveness
 550 plane and presented as cost-effectiveness acceptability curves to show the probability of the
 551 intervention being cost-effective at a range of willingness-to-pay threshold levels. A sensitivity
 552 analysis will be conducted to take account of uncertainty and imprecision in the measurements,
 553 including multiple imputation models for missing values.

554 **Qualitative process evaluation**

555 Qualitative methods will be used to assess assumptions underlying the intervention strategy. In-
 556 Depth Interviews (IDIs) and Focus Group Discussion (FGDs) will explore key program
 557 implementation outcome variables and will cover intervention: acceptability, feasibility,
 558 appropriateness (including cultural appropriateness), fidelity, adoption and participants' view
 559 about intervention's perceived impact (both negative and positive) and ethics and safety concerns
 560 (Proctor, 2009). Following well-established procedures, qualitative interviews will be recorded,
 561 transcribed in Urdu and analysed in the original language (translation into English will only take
 562 place for the purpose of international reporting). IDIs and FGDs will be conducted at the preferred
 563 venue of the respondents, whether at home, at school, or at any other place of convenience where
 564 privacy for IDIs / FGDs can be assured.

565 **Sampling:** Interviews will be conducted with both adolescents and caregivers in the intervention
 566 including completers and drop outs, non-specialist facilitators, supervisory and school staff
 567 (teachers and head teachers). Sampling for qualitative interviews will be purposive based upon
 568 the knowledge and exposure to EASE for each category of respondent. Sampling for in-depth
 569 interviews will continue until theoretical saturation has been reached, anticipated to require 8 – 15
 570 interviews with each category of respondent.

571 IDIs and FGDs will be conducted by the qualitative research team who will be trained in the key
 572 principles of qualitative interviewing. One interviewer will ask the questions and the other will
 573 take notes of the interview. Audio recordings will also be taken. All data will be anonymised and
 574 no identifying information will be collected during the interview. The interviews will follow a
 575 semi-structured interview guide addressing topics relevant to each category of respondents (Table
 576 2).

577

578 **Table 2:** EASE semi structured interview summary guide

Sample	Themes
Non-specialist facilitators (delivery agents in EASE)	Intervention's acceptability, feasibility, appropriateness (including cultural appropriateness), fidelity, adoption, intervention's perceived impact (both negative and positive), ethics and safety concerns
Beneficiaries (adolescents in EASE)	Intervention's acceptability, feasibility, appropriateness (including cultural appropriateness), adoption, intervention's perceived impact (both negative and positive) and safety concerns
Beneficiaries (caregivers in EASE)	Intervention's acceptability, feasibility, appropriateness (including cultural appropriateness), adoption, intervention's perceived impact (both negative and positive) and safety concerns
Supervisory staff	Intervention's acceptability, feasibility, appropriateness (including cultural appropriateness), fidelity, adoption, intervention's perceived impact (both negative and positive), ethics and safety concerns
School staff	Barriers and facilitator of implementing intervention in school settings including perceived impact of intervention (both negative and positive)

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581 Analysis of in-depth interviews will be thematic, aided by application of the framework approach
582 (38), which complements applied research, offers transparency in the analysis process, and has an
583 ability to move from descriptive narrative accounts to conceptual explanations. Analysis will move
584 through phases of familiarisation, generation of codes, and selection of illustrative quotes (39),
585 conducted by multiple members of the qualitative research team. Data from FDGs and IDIs will
586 be triangulated to ensure a comprehensive understanding through convergence or divergence of
587 findings relating to each topic explored in interviews.

588 **Trial management**

589 The Trial Steering Committee (TSC) comprising of Principal Investigator (PI), Co-Investigator
590 (s), trial coordinator, senior researchers and intervention staff who will meet monthly to oversight
591 the study and manage the trial.

592 **Ethics**

593 Ethical approval for the current study was obtained from Central Ethics Committee of University
594 of Liverpool, UK, Ethics Review Committee of World Health Organization (WHO) Geneva and
595 from Human Development Research Foundation Institutional Review Board, Islamabad, Pakistan.
596 Data collection will be proceeded after seeking informed from the primary caregiver and assent
597 from adolescents. All of the team members will be trained to ensure safety and confidentiality of
598 participants throughout the research. An independent Trial Steering Committee (TSC) will be set-
599 up to ensure human subject protection to the highest standards.

600 **Dissemination**

601 The dissemination of intervention will be carried through peer reviewed publications and training
602 to the relevant institutions to inform the Education and Health Ministries of Pakistan, in order to
603 scale-up program to public sector education. In addition to that the results will be disseminated
604 through WHO's media channels (40). The results of this study will be disseminated in Urdu to
605 community key stakeholders (such as participant school head teachers, children and
606 parents/primary caregivers) through reports or community presentations.

607

608 **Figure 1:** Flow of participants through cRCT

609

610 **Acknowledgment**

611 The study sponsor and funders have no role in the study design; collection, management,
612 analysis, and interpretation of data; writing of the report; and the decision to submit the report
613 for publication.

614

615 **Authors' contributions:** AR (Principal Investigator) conceived the study and was involved in
616 developing the research design and supervising all aspects of the study. SUH (Co-Principal
617 Investigator) was involved in conception of the study, developing the research design, study
618 protocol, finalising the study tools, training and day-to-day supervision of the study team in
619 Pakistan and drafted the initial manuscript. DW (Co-Investigator) was responsible for all the
620 statistical aspects of the study including development of the statistical analysis plan. ZeH (trial
621 coordinator) worked with UH to develop the research design, study protocol, finalising the study
622 tools, training and day-to-day supervision of the study team and drafted the manuscript. AM, ATN,
623 UB, NS, HJ, MvO, SM, SAK and FAM contributed to the writing.

624 All authors read and approved the final manuscript.

625
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629
630 **Competing interests:** None declared.

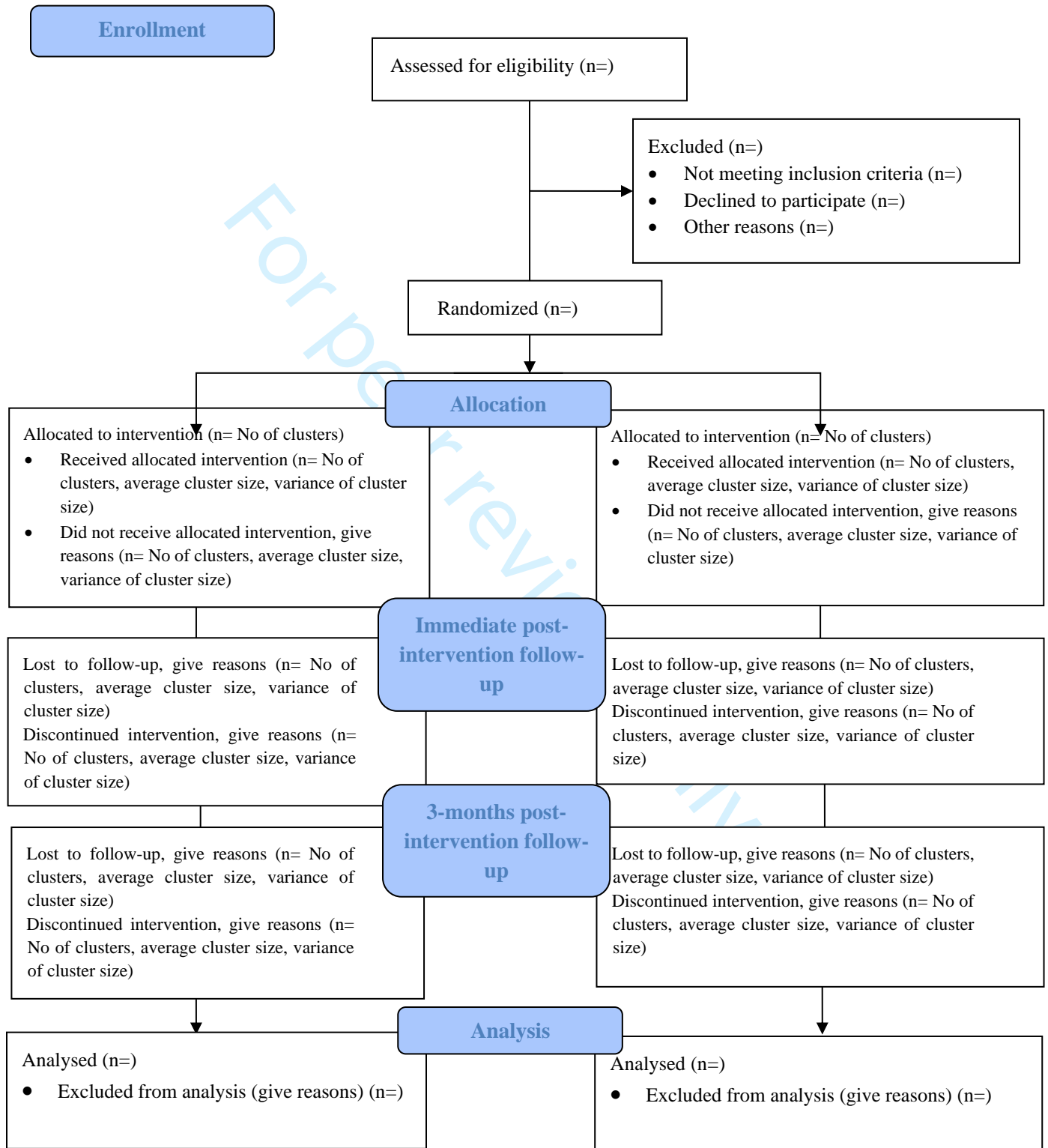
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Figure 1: Flow of participants through cRCT





STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	Title p.1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	Abstract p. 2
	2b	All items from the World Health Organization Trial Registration Data Set	Included in the registration
Protocol version	3	Date and version identifier	N/A
Funding	4	Sources and types of financial, material, and other support	19
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1 & 18
	5b	Name and contact information for the trial sponsor	N/A
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	18
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	15

1	Introduction			
2				
3	Background and	6a	Description of research question and justification for undertaking the trial, including summary of relevant	6-7
4	rationale		studies (published and unpublished) examining benefits and harms for each intervention	
5				
6		6b	Explanation for choice of comparator	10
7				
8	Objectives	7	Specific objectives or hypotheses	7
9				
10	Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group),	7 & 14
11			allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	
12				
13				
14	Methods: Participants, interventions, and outcomes			
15				
16	Study setting	9	Description of study settings (e.g., community clinic, academic hospital) and list of countries where data will	7&8
17			be collected. Reference to where list of study sites can be obtained	
18				
19	Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and	8
20			individuals who will perform the interventions (eg, surgeons, psychotherapists)	
21				
22	Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be	9-10
23			administered	
24				
25		11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose	N/A
26			change in response to harms, participant request, or improving/worsening disease)	
27				
28		11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence	N/A
29			(eg, drug tablet return, laboratory tests)	
30				
31		11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	10
32				
33	Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood	10-13
34			pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg,	
35			median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen	
36			efficacy and harm outcomes is strongly recommended	
37				
38	Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for	11
39			participants. A schematic diagram is highly recommended (see Figure)	
40				
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1	Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	8-9
2				
3				
4	Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	9
5				
6	Methods: Assignment of interventions (for controlled trials)			
7	Allocation:			
8				
9				
10	Sequence generation	16a	Method of generating the allocation sequence (e.g., computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	14
11				
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16	Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (e.g., central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	14
17				
18				
19				
20	Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	14
21				
22				
23				
24	Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	14
25				
26				
27		17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	14
28				
29				
30				
31	Methods: Data collection, management, and analysis			
32				
33	Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	15&16
34				
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38		18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	N/A
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1	Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	15&16
2				
3				
4				
5	Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	15-17
6				
7				
8		20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	15-17
9				
10		20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	16-17
11				
12				
13				
14	Methods: Monitoring			
15				
16	Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	18-19
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22		21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	N/A
23				
24				
25	Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	15
26				
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28	Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	N/A
29				
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32	Ethics and dissemination			
33				
34	Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	18
35				
36				
37	Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	N/A
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1	Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	9
2				
3				
4		26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	N/A
5				
6				
7	Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	15
8				
9				
10	Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	19
11				
12				
13	Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	18
14				
15				
16	Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	N/A
17				
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20	Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, health care professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	18
21				
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24		31b	Authorship eligibility guidelines and any intended use of professional writers	N/A
25				
26		31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	N/A
27				
28				
29	Appendices			
30				
31	Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	N/A
32				
33				
34	Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	N/A
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*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "[Attribution-NonCommercial-NoDerivs 3.0 Unported](https://creativecommons.org/licenses/by/4.0/)" license.