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START adolescents: study protocol of a randomised controlled trial to investigate the efficacy of a low-threshold group treatment programme in traumatised adolescent refugees

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ABSTRACT

Introduction No evaluated therapeutic approaches, that can efficiently be established in routine mental healthcare, are currently available for traumatised adolescent refugees in Germany. This study evaluates the efficacy of the Stress-Traumasymptoms-Arousal-Regulation-Treatment (START) programme to reduce trauma-related symptoms and psychological distress in traumatised adolescent refugees based in Germany.

Methods and analysis This randomised, waiting-list-controlled, multicentre trial with a 12-week follow-up will include 174 refugee minors with partial or full post-traumatic stress disorder who are fluent in either Arabic, Dari, English, German or Somali. Eligible refugee minors will be randomised to the START or waiting-list control groups. The manualised 8-week START programme is based on techniques of dialectical behaviour therapy (DBT), fosters adaptive coping with emotional distress and traumatic symptoms and comprises eight therapy modules and a booster session. Study assessments are planned at baseline, post-treatment (ie, after programme participation or waiting time), booster session at week 12 or 12-week waiting time, and at the 12-week follow-up. Primary and coprimary outcomes are changes in psychological distress and traumatic symptoms at post-treatment and will be analysed as response variables in linear mixed regression models. Secondary outcomes are changes in further trauma-related and other psychopathological symptoms, emotion regulation and intermediate effects of the programme at follow-up. We will also assess effects of the programme with ecological momentary assessments and on neuroendocrine stress parameters using hair cortisol.

Ethics and dissemination This study has been approved by the lead ethics committee of Rhineland-Palatinate and the ethics committees of participating sites. The study results will be disseminated through peer-reviewed publications and scientific conferences.

Trial registration number DRKS00020771.

Strengths and limitations of this study

- Randomised waiting-list controlled multicentre trial with follow-up.
- Manualised DBT-based psychotherapeutic programme with patient material available in Arabic, Dari, English, German and Somali.
- Multimodal assessment approach of intervention effects on symptoms, functioning and daily living outcomes by psychometric evaluations, electronic ambulatory assessments (e-diaries) and neuroendocrine stress parameters.
- Restriction of study participation to refugee minors with language skills in Arabic, Dari, English, German and Somali.

BACKGROUND AND RATIONALE

Among the forcibly displaced persons worldwide there is a high number of children and adolescents under the age of 18 years.[1] At the peak of the refugee influx in Germany in 2016, 261 386 of the 745 545 asylum applications recorded in total were filed from refugees under the age of 18 of which 49 786 applications were filed from unaccompanied refugee minors in the care of youth welfare services and without the company of parents or persons with the right of custody. The high percentage of asylum applications filed by refugee minors has remained stable since then though due to political changes the total number of refugees entering Germany has steadily decreased.[2 3] Of all refugees, children and adolescents, and especially unaccompanied refugee minors, are the most vulnerable group. They are at particular risk of traumatisation before, during and after their flight as well as for mental health

problems.[4–6] Children and adolescents seeking asylum in Germany report an average of eight potentially traumatic experiences, with 98% of unaccompanied refugee minors reporting traumatic events.[5–7] They are exposed to stress due to insecure legal status and adaptation to new environments, cultural demands and language, the loss of stability provided by their cultural background of origin as well as provided by their families and caregivers if unaccompanied.[8] In addition to their often prevalent traumatisation, they are also confronted with age-related developmental tasks like peer group integration, identity formation, education, professional training and finding their role in the host society. Cross-sectional studies and reviews assessing mental health problems in refugee minors report prevalence rates of 17%–71% for post-traumatic stress disorder (PTSD), 12%–44% for depressive disorders, 18%–38% for anxiety disorders and 33%–72% for behaviour problems.[9 10] Longitudinal studies suggest a high risk of chronic mental health problems and indicate that baseline symptom severity, sex, being unaccompanied and post-migration factors like asylum status and access to mental healthcare are predictors of future mental health status.[6 11] Studies evaluating trauma-related therapy programmes in refugee minors have mostly reported significant effects on trauma and/or additional mental health symptoms. However, conclusive interpretation of the findings is limited by heterogeneous therapy approaches, lack of manualised programmes and methodological shortcomings like lack of power analyses, randomisation and control groups, small sample sizes or heterogeneous study settings such as clinical, school or community settings in high-income countries, but also refugee camps in war regions.[12–17] Evidence from rigorous methodological approaches like randomised controlled trials (RCTs) is needed to cross-validate the available results in terms of validity, reliability, and generalisability of the programmes.

STUDY OBJECTIVES

The manualised Stress-Traumasymptoms-Arousal-Regulation-Treatment (START) programme was developed from clinical work with traumatised unaccompanied refugee minors in Germany to promote coping with traumatic distress and emotional irritability.[18–20] An uncontrolled pilot study in 22 traumatised refugee minors showed positive effects on emotion regulation, adaptive strategies, self-control, distress and good feasibility.[18] A subsequent study confirmed the positive effects on adaptive emotion regulation strategies.[21]

The primary aim of this RCT is to evaluate the efficacy of the START programme in reducing psychological distress and trauma symptoms in traumatised adolescent refugees compared with a waiting-list control group (WL). Main secondary aims are to assess whether treatment effects will remain stable for at least 12 weeks after programme termination (follow-up at week 24) and to assess whether the participants of the START groups improve emotion regulation strategies and mental health compared with WL. As stress and emotions are context-dependent and highly dynamic,[22] intervention effects are assessed by psychometric instruments and with electronic ambulatory assessment (e-diaries). Ambulatory assessment aims to reduce retrospective biases while gathering ecologically valid data from everyday life near real-time. It has been shown as superior to retrospective psychometric assessment in terms of predicting symptom and treatment outcome[23–26] and assessing reliably everyday functioning.[27] We also evaluate intervention effects on the neuroendocrine stress system by assessing hair cortisol, which reflects the cumulative cortisol release over the past months and has been shown to capture treatment effects in PTSD.[28]

The study is part of the START research consortium, which evaluates distress-reducing psychotherapeutic group and preventive family interventions in traumatised toddler, adolescent and young adult refugees and aims to contribute to improved evidence-based therapeutic interventions for refugees within a stepped mental healthcare approach. The consortium comprises the START Adolescent Study, the START Childcare Study,[29] the START Young Adults Study, and the smartphone-based experience sampling study tracking symptoms and daily living functioning with the use of e-diaries across the START Adolescents and Childcare studies. For further information regarding the consortium, please see wwwmentalhealth4refugeesde. The presented paper reports on the START Adolescents protocol (V.4.0, 16 March 2020) and has been conceived according to the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) guidelines.[30 31] Please also refer to SPIRIT checklist (online supplemental file 1) and to table 1.

Methods and analysis

Patient and public involvement

The original START programme was developed from clinical work with highly traumatised unaccompanied refugee minors of different countries of origin, who had recently arrived in Germany.[18–20] The adapted and extended version of the programme, that is evaluated in this RCT, was redesigned according to the participants' feedback of the pilot study groups, who were also traumatised refugee minors from different countries of origin. The public was not involved when designing the study.

Trial design and setting

The study is conducted as a 12weeks, two-arm, randomised, WL-controlled, multicentre trial with a 12-week follow-up and six participating outpatient departments in Germany, all of which are experienced in treating traumatised adolescent refugees. The study is coordinated by the Department of Child and Adolescent Psychiatry and Psychotherapy, University Medical Center, Johannes Gutenberg University, Mainz, Germany. The study intervention comprises an adapted version of the START programme.[18–20] Languages used in the study for the intervention and the assessments are Arabic, Dari, English, German or Somali. Interpreters are

Table 1 SPIRIT flow diagram

	Study period				
Time point	Screening	T0 Study visit Baseline 1 week after random. (WL) or before START Programme	T1 Study visit 8 weeks after T0 (WL) or after START Programme	T2 Study visit 4 weeks after T1 (WL) or at booster session (START)	T3 Study visit Follow-up 12 weeks after T2
Enrolment					
Eligibility screen	X				
Informed consent	X				
Randomisation	X				
Assessments					
Demographic data	X				
Medical history	X				
Medication/ psychotherapy	X	X	X	X	X
Saliva drug screening	X				
TONI-4	X				
ETI-CA	X		X	X	X
K-SADS-PL	X				
CGI-S	X		X	X	X
C-SSRS	X		X	X	X
REB		Weekly			
AUDIT	X				
Endangerm. to others	X		X	X	X
PSS-10	X	X	X	X	X
IES-R	X	X	X	X	X
SDQ self		X	X	X	X
SDQ caregiver	X		X	X	X
BDI-II		X	X	X	X
DERS18		X	X	X	X
cPTCI		X	X	X	X
CATS-2		X	X	X	X
DDNSI		X	X	X	X
PMLD		X			
Therapy expectation		X			
E-Diaries		X	X	X	X
Hair cortisol		X		X	X
AE assessments		X	X	X	X
Intervention					
START programme					
Booster session					

AEs, adverse events; AUDIT, Alcohol Use Disorders Identification Test; BDI-II, Beck Depression Inventory, second edition; CATS-2, Child and Adolescent Trauma Screen-2; CGI-S, Clinical Global Impression Scale, severity of illness subscale ; cPTCI, Post-traumatic Cognitions Inventory-child version; C-SSRS, Columbia-Suicide Severity Rating Scale; DDNSI, Disturbing Dream and Nightmare Severity Index; DERS-18, Difficulties in Emotion Regulation Scale, 18-Item; ETI-CA, Essen Trauma Inventory for Children and Adolescents; IES-R, Impact of Event Scale-Revised; K-SADS-PL, Kiddie-Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime; PMLD, Post-Migration Living Difficulties Questionnaire; PSS-10, Perceived Stress Scale, 10-Item; SDQ, Strengths and Difficulties Questionnaire; SPIRIT, Standard Protocol Items: Recommendations for Interventional Trials; START, Stress-Traumasymptoms-Arousal-Regulation-Treatment; TONI 4, Test of Nonverbal Intelligence, Fourth Edition; WL, waiting-list.

involved if needed. The study is not blinded for the treatment condition, which will be evident to participants, caregivers and study therapists. Recruitment started 1 October 2020. We expect that the last participants will complete the study end of October 2022. Data base lock and analysis of primary outcomes are planned until end of December 2022.

Key stopping rules for patients are a withdrawal of informed consent, unwillingness to further participate in the trial, any factors affecting the patient's or others' well-being, for example, acute suicidality or acute endangerment to others, onset of other acute severe mental disorders, alcohol or substance abuse, inpatient treatment of over 2 days, start of concurrent psychotherapy and more than two psychotherapeutic crisis interventions. Key stopping rules for participating centres are non-adherence with the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use: Guidelines for Good Clinical Practice (ICH-GCP)[32] or the study protocol, insufficient recruitment of participants, or insufficient data quality. The key stopping rule of the trial is a change in the overall risk-benefit ratio.

PARTICIPANTS

We will allocate 174 participants to the trial and expect that we will have to screen 240 adolescent refugees for eligibility. Inclusion criteria are: informed consent by adolescents and caregivers, flight background, age between 13.00 and 17.11 years, verbal communication skills and reading comprehension in one of the study languages, non-verbal IQ ≥70, partial or full PTSD, PTSD symptoms are the clinically most impairing condition with at least moderate clinical symptom severity. We kept the exclusion criteria to a minimum, to foster the applicability of the programme in routine care as much as possible. Exclusion criteria are: current substance use disorder and/or harmful alcohol abuse, primary severe mental disorders other than PTSD, acute suicidality or danger to others, unstable psychotropic medication (change of psychotropic medication within the last 2 weeks before baseline assessment), current ongoing psychotherapy, inpatient status or study participation in another clinical trial, unaccompanied refugee minor without a legal representative, known pregnancy. Participants, who attend all assessment visits, will be given a study compensation. Participants will be insured by a clinical trial insurance during the time of study participation. Please see for detailed information about the assessment of eligibility criteria also the sections 'screening' and 'psychometric instruments'. The participants' study flow is provided in figure 1.

STUDY CONDUCT

Recruitment

For recruitment, study information is provided to schools, child and adolescent psychotherapists/psychiatrists, social workers, youth welfare providers, at conferences, professional working group meetings, in newspaper articles or interviews, on the institutions' homepages and on social media. All participants' information about the

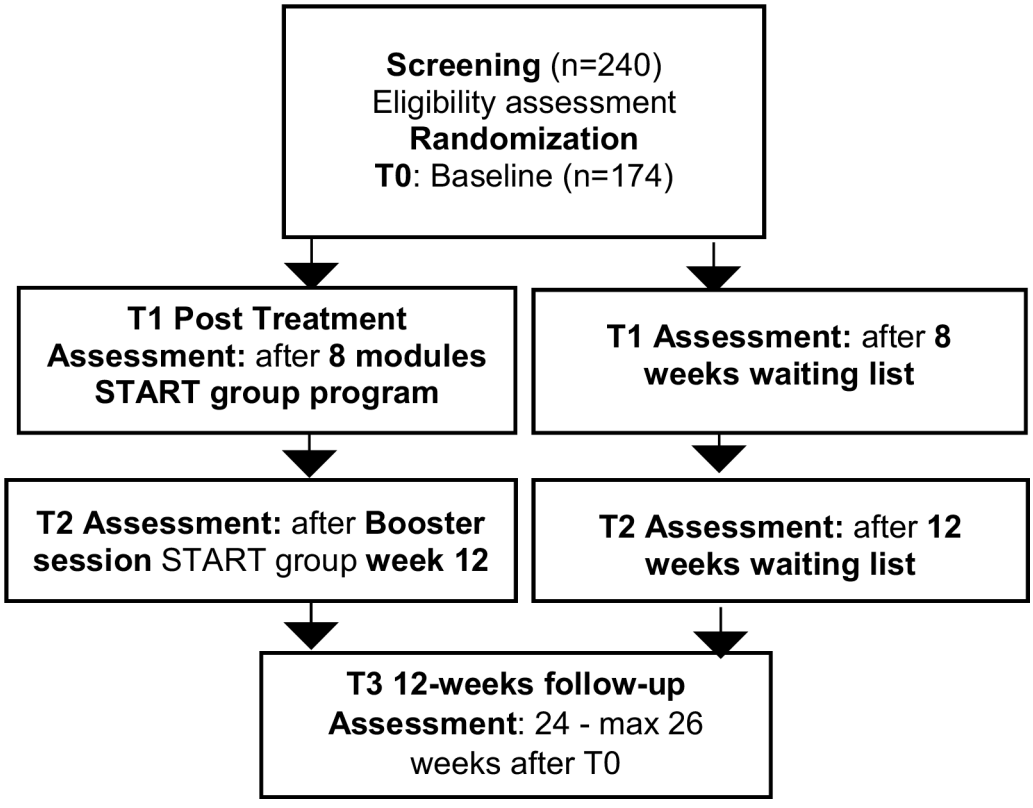

Figure 1 Participants' study flow. START, Stress-Traumasymptoms-Arousal-Regulation-Treatment.

study is provided in a caregiver and adolescents' version in all study languages.

Trial flow

For a summary of trial flow and assessment visits please see the SPIRIT flow diagram, table 1. All assessments are provided by trained study staff and are performed at the screening visit, baseline (T0), post-treatment (after 8-week START programme or 8-week waiting time; T1), after the booster session or 12-week waiting time (T2), and after 24 weeks at the 12-week follow-up (T3). The maximum time allowed between T0 and T3 is 26 weeks. After termination of the study, all participants are informed about their current diagnostic status and available interventions provided by child and adolescent psychiatric and psychotherapeutic routine care. Participants of the WL are given the opportunity to take part in independent START groups.

Screening visit

Assessment of informed consent for study participation, inclusion and exclusion criteria, demographic and medical data. Inclusion of eligible participants, randomisation to the intervention (START) or WL using a web-based randomisation system with permuted blocks stratified by centre (http://randomizer.at).

Baseline (T0), post-treatment (T1), booster session (T2), 12-week follow-up (T3) assessments

T0 takes place between one and 2 weeks after randomisation (WL) or before the first programme session (START), T1 within 1 week after the 8-week programme (START) or within 8–9 weeks after T0 (WL), T2 within 1 week after the booster session (START) or 4–5 weeks after T1 (WL) and T3 follow-up visits within 12 weeks after T2 (START/WL). At T0 only, the Post-Migration Living Difficulties Questionnaire (PMLD) and Questionnaire on Therapy Expectation are assessed. At the T0(T1)–T3 visits primary endpoints, trauma symptoms, emotion regulation, general psychopathology, overall clinical severity of mental disorders, suicidality and endangerment to others are assessed and 1 week e-diaries are applied. Hair cortisol is assessed at T0, T2 and T3. Adverse events are assessed at T0–T3 visits and weekly until T1.

Intervention

Details of the START Adolescents programme are provided in table 2. START Adolescents study groups comprise three to eight participants and are restricted to study participants, who have been randomised to the intervention group. The manualised START group programme is based on DBT-techniques with emphasis on coping with emotional distress and traumatic symptoms, resilience, adaptive functioning and self-efficacy, but not on confrontation with traumatic memories. The group therapy is provided by two therapists through twice-weekly 60 min sessions and interactions are based on validation and acceptance techniques. Written participant programme materials are available in all study languages and if necessary, translators will attend the group therapies.

The original START Adolescents programme comprised five modules with psychoeducation on trauma, stress, distressing emotions and crises, mindfulness training, arousal regulation, stress reduction techniques, and handling nightmares. For the current study, the START manual[18–20] was extended by the three additional modules 6–8 and a booster session. The additional modules provide an intensified training of stress reduction skills, mindfulness techniques and additional psychoeducation about emotions and interpersonal effectiveness. Each session follows a defined structure and comprises, as fixed repeated elements, mindfulness training, monitoring one's own inner tension/stress ('stress signal light'), reviewing experiences when applying the programme skills, new contents/psychoeducation and skills training. The final session in module 8 is dedicated to a farewell ceremony and to validating and rewarding the participants' efforts and achievements. During the booster session, which is scheduled 4 weeks after programme termination, participants review their experiences when applying the acquired skills and techniques, their open needs, and provide an outlook on their personal future wishes and goals. If standardised risk assessments or participants' personal information reveal acute danger to the self or others, additional psychotherapeutic crisis interventions will be offered to the participant. Participants with ongoing acute suicidal tendencies or ongoing danger to others after two subsequent crisis interventions must be excluded from study participation and transferred to specific intense psychiatric care.

ASSESSMENTS

Psychometric instruments

For details of the instruments including psychometric properties, please see online supplemental file 2. All self-report assessments are applied in the study languages, all interviews are applied with the help of interpreters if indicated.

Inclusion and exclusion criteria

Inclusion and exclusion criteria are assessed with the Essen Trauma Inventory for Children and Adolescents,[33] Clinical Global Impression Scale, severity of illness subscale (CGI-S[34]), the Kiddie-Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime version,[35–37] the Alcohol Use Disorders Identification Test,[38] the Columbia-Suicide Severity Rating Scale,[39] the Test of Nonverbal Intelligence, Fourth Edition,[40] and the standardised Questionnaire to Assess Endangerment to Others.[39]

Primary endpoints

Psychological distress is assessed with the Perceived Stress Scale, 10-item version (PSS-10), a validated self-report questionnaire, that measures the intensity with which individuals appraise their daily life as stressful, unpredictable, uncontrollable and overloaded. Reliability and validity

Table 2 Start adolescents programme, modules 1–8 and booster session

Before beginning of START: Written patient information. Handout.
Every session: Mindfulness practice and stress signal light. Discussing between-session skills practice. Written patient material.
Between the sessions: Participants are asked to train skills and techniques.

	Key interventions	Practice/training techniques
Module 1 Week 1 Sessions 1 and 2	Welcome. Introduction to START. Introduction of participants. Psychoeducation. Explanation of the concepts stress, high stress and stress-regulation skills. Teaching techniques. Skills for reducing distress and high distress. Relaxation techniques.	High-stress skills. Progressive muscle relaxation.
Module 2 Week 2 Sessions 3 and 4	Consolidation**:** Available skills. Teaching techniques. Stress signal light for stress/inner tension monitoring and awareness. Emotion regulation strategies: mindful senses (hearing, feeling, tasting, watching, smelling). Skills box.	Mindful sensual experiences. Individual stress signal lights. Individual stimuli for distress/euthymia. High-stress skills. Individual skills boxes.
Module 3 Week 3 Sessions 5 and 6	Consolidation. Individual skills boxes. Teaching techniques. Skills chains. Individual red light. Self-empowerment/resilience.	Skills chains Self-empowerment
Module 4 Week 4 Sessions 7 and 8	Consolidation. Available skills. Psychoeducation. Explanation of the concept of crisis and management of crisis. Teaching techniques. Managing crisis: acceptance/skills/safe place. Managing flashbacks. Safety and emergency card. How to recognise change. How to change the moment?	Recognition and managing of crisis. Individual safe place. Skills that change the moment.
Module 5 Week 5 Sessions 9 and 10	Consolidation. Available skills. Psychoeducation. Sleep disturbances and nightmares. Teaching techniques. Managing nightmares.	Telling/writing nightmares. Skills for managing nightmares.
Module 6 Week 6 Sessions 11 and 12	Consolidation. Available skills. Psychoeducation. Emotions and emotion awareness. Teaching techniques. Emotion surfing 'Letting go of emotional suffering'.	Recognising and naming emotions (emotion cards). Individual pleasant and unpleasant emotions. Emotion surfing.
Module 7 Week 7 Sessions 13 and 14	Consolidation. Available skills, emotion recognition and understanding. Psychoeducation. Emotional network: Interdependence of emotions, thinking, behaviour and prompting stimuli. Skills for emotion regulation.	Role-play/competition: Recognising emotions and thoughts. Understand, name and regulate emotions and related behaviour and thoughts.
Module 8 Week 8 Sessions 15 and 16	Review and consolidation: Available skills, current difficulties. Crisis plan. Close-out. Farewell celebration. Awarding the participants. Certificates: 'You did your very best.' Outlook to booster session.	Experiencing acquired/activated resources (balloon game). Discussing individual skills lists, open needs. Discussing crisis plan/designing emergency cards.
Booster Session Week 12 Session 17	Review and consolidation: Helpful skills, difficulties with skills practice within the last 4 weeks, current open needs. Small symbolic gift, for example, little gemstone.	Outlook for future/participants' wishes/practicing how 'to turn the tide'.

START, Stress-Traumasymptoms-Arousal-Regulation-Treatment.

for the Arabic, English and German version have been shown to be sufficient or good.[41–44] Traumatic symptoms are assessed with the Impact of Event Scale-Revised (IES-R), a validated, self-report questionnaire evaluating traumatic symptoms on the subscales intrusion, avoidance, hyperarousal and on an overall measure of traumatic distress. Reliability and validity for the Arabic, English and German version have been shown to be good.[45–48]

Secondary endpoints

We assess trauma-related psychosocial impairment and PTSD criteria according to Diagnostic and Statistical Manual of Mental Disorders, 5th ed. (DSM-5) with the Child and Adolescent Trauma Screen-2,[49] trauma-related cognitions with the Posttraumatic Cognitions Inventory-child version[50–52] and frequency and intensity of nightmares with the Disturbing Dream and Nightmare Severity Index.[53 54] Emotion regulation is assessed with the 18-item version of the Difficulties in Emotion Regulation Scale (DERS-18[55]), general psychopathology with the Strengths and Difficulties Questionnaire,[56 57] and the Beck Depression Inventory, second edition.[58 59] Overall severity of illness is assessed with the CGI-S.[34]

Additional psychometric assessments

We assess adverse life experiences related to migration with the adapted German version of the self-rated PMLD,[60 61] and therapy expectations with a self-designed questionnaire comprising three questions that are answered on a 5-point Likert-type scale.

Ambulatory momentary assessment: electronic diaries

We use smartphone-based electronic (e)-diaries to assess aversive inner tension, emotional intensity, trauma symptoms (intrusions, hypervigilance), cognitive and behavioural avoidance of triggering situations in daily environments, sleep quality, stressfulness, content and number of nightmares, self-efficacy, self-esteem, rumination and somatisation.[62–64] Filling in the answers takes a few minutes and items are available in all study languages. Rumination about cultural differences, social support and conflicts, discrimination experiences, and personally important events at school will be used as context variables to determine their associations with emotional distress and trauma symptoms. Participants receive a comprehensive explanation of the use of e-diaries as a spoken PowerPoint presentation and a written document in each participant's respective language. After the presentation, the participant is asked to do a test trial on the smartphone. Smartphones are programmed with the e-diary app movisensXS[65] and employ an hourly 1-week time-based e-diary design. Prompts are pseudorandomised within a time frame of 50–70 min to avoid expectancy effects. At the beginning of the study, participants are asked to enter their school schedules and determine their first prompt in the morning. On the weekends, e-diary assessments start at 10:00 hours no data are assessed during school hours. The prompts end at about 21:00 hours on school days and about 22:00 hours if there is no school the next day.

Hair cortisol

If additional informed consent for hair cortisol collection is provided by study participants and their legal representatives, we collect thin hair strands from the posterior vertex of the head cut as close to the scalp as possible. Hair strands are tied together, sealed, and stored in a dry and dark place. Prior to analyses, they will be cut into a 2 cm segment proximal to the scalp, representing cumulative cortisol secretion of the last 2 months.[66]

Quality assurance and monitoring

The study procedures are monitored by the Coordination Centre for Clinical Trials (KKS) Heidelberg according to the ICH-GCP[32] with respect to a risk-based quality management strategy and ensure that the trial is conducted according to protocol and regulatory requirements. All data of the ongoing study are reviewed by an independent data monitoring committee once a year with special focus on safety issues.

Manual adherence across different therapists and participating centres is ensured by training all therapists on the START Adolescents programme and regular supervision with standardised assessments of manual adherence. We require a certain level of professional training from the therapists, of whom at least one per group must be a graduated psychologist, pedagogue, or physician.

The quality of psychometric assessments, tests and interviews is ensured by training the raters on the study assessments. Raters must have a bachelor's or master's degree in psychology or a comparable standard. Raters with a bachelor's degree in psychology will administer questionnaires and psychological tests, raters with a Master's degree in psychology will administer the study interviews.

DATA MANAGEMENT

The KKS Heidelberg is responsible for data management and analysis as well as data security and data transfer processes. All procedures are implemented in accordance with ICH-GCP guidelines and the Declaration of Helsinki.[32 67] The protection of private data is ensured by a pseudonymisation procedure, and all private data are handled with respect to the European General Data Protection Regulation.[68] Data are assessed by an electronic case report form (eCRF) and paper-based self-report questionnaires. The latter are transferred in copy to the KKS Heidelberg for double entry into the eCRF. E-diary data are transferred to the Mental mHealth lab, Karlsruhe Institute of Technology, analysed there and saved in encrypted form. The smartphones for e-diaries are provided by the research facility; no private smartphones are used for study purposes.

Data availability

The research data generated during this study will be available on reasonable request by the study coordinating centre at the Department of Child and Adolescent Psychiatry, University Medical Center, Mainz, Germany. Anonymised data use by other researchers not involved in the study may be done with prior agreement.

STATISTICS

Sample size calculation

The sample size calculation is based on the coprimary outcomes of emotional distress (PSS-10) and traumatic symptoms (IES-R) at T1. Based on available studies[69 70] we assume in our study an effect size of d=0.63 for the PSS-10 and of d=0.56 for the IES-R score at T1. This results in a required sample size of n=84 (PSS-10) and n=104 (IES-R) for a one-sided test at an α=0.025 level with a power of 80% to detect such differences. The START pilot trial showed a drop-out rate <10% and was conducted as a one-centre single-arm naturalistic trial with mostly inpatients.[20] We, therefore, calculated the sample size on the assumption of 40% drop-outs between T0 and T1 to account for the multicentre, WL-controlled approach and unstable living conditions of the included population. This amounts to n=174 participants who need to be randomised in our trial.

Analysis population and analysis

All randomised participants will be included in the full-analysis set as allocated. All randomised participants, who finish the study according to the study protocol until T2 as planned with no missing values for T1 (primary endpoint) will be included in the per-protocol set for analysis as allocated. All randomised participants will be included in the safety population according to the applied intervention.

Baseline characteristics will be analysed descriptively for the safety, full-analysis, and per-protocol set in the intervention and control group. The primary and coprimary endpoints will be analysed in the full-analysis set. Missing values will be imputed. Endpoints will be assessed as response variables in linear mixed regression models with site and psychotherapeutic group as random effects, intervention group, sex and region of origin as fixed effects, and age, PSS-10 and IES-R baseline scores, respectively, as linear effects with a hierarchical testing procedure that maintains the overall significance level of α=0.025. The primary analysis will be repeated in the per-protocol population as a sensitivity analysis. Since the different timing of the T0 baseline examination in the study groups after randomisation could cause biases in the effect estimates, that cannot be estimated or modelled, additional sensitivity analyses will be performed, such as repeating the primary analysis using the screening value instead of the baseline value. Secondary outcomes will be analysed in the full-analysis set. Missing values will not be imputed. The stability of treatment effects up to T3 will be assessed by calculating confidence intervals on the T1–T3 and T2–T3 difference for the PSS-10 and IES-R total scores in the intervention group. Psychometric scales used for assessment of secondary outcomes and hair cortisol concentrations will be analysed according to primary endpoints or descriptively. For the analysis of e-diary data, multilevel models will be used to characterise momentary mechanisms and context-dependent affective experiences, which allow a nested data structure (momentary experiences within participants), and enable different numbers of ratings per participant to be handled quite well.[71] Safety variables will be analysed in the safety and full-analysis population.

Ethics and dissemination

The study protocol, patient recruitment procedures, patients' information and informed consent material have been approved by the lead ethics committee of Rhineland-Palatinate (ID 2019-14709) and the ethics committees of participating sites. For every substantial protocol modification approval of all ethics committees is required. The study will be conducted according to ICH-GCP[32] and the Declaration of Helsinki.[67] Study results will be published through peer-reviewed publications and presented at scientific and clinical conferences.

TRIAL STATUS

Recruitment started 1 October 2020.

DISCUSSION

Evidence-based, evaluated, low-threshold and culture-sensitive psychotherapeutic treatment programmes, that reduce distress caused by traumatic experiences that can be efficiently established in routine mental health-care, would represent valuable therapeutic interventions to support refugee minors with trauma-related symptoms and emotion regulation difficulties. However, such interventions are currently lacking. The primary aim of this study is to evaluate the clinical efficacy and intermediate outcome of the distress-reducing psychotherapeutic START programme and to contribute to improved evidence-based therapeutic interventions for adolescent refugees within a stepped-care mental health approach in Germany. If shown to be effective, the first rigorously evaluated manualised intervention programme for traumatised adolescent refugees will be available, which will have widespread implications for clinical practice.

Some limitations for the application of the programme in mental health routine care in host countries may be that the therapeutic study groups are limited only to traumatised refugees, which may not reflect clinical reality. Another limitation is the restriction of study participation to refugee minors with language skills in Arabic, Dari, English, German and Somali. Thus, the study will not provide information on the effectiveness of the programme if applied to refugee minors with a different cultural or language background. However, since all

programme materials are available in Arabic, Dari, English, German and Somali, the START programme will provide a treatment option not only in German-speaking or English-speaking host countries that care for refugee minors but also in refugee camps based in Arabic-speaking, Dari-speaking or Somali-speaking countries, where is a huge need for easy-to-apply psychotherapeutic treatment options.

Beyond effects on the symptom level, we will analyse intervention effects on psychosocial functioning and everyday behaviour through the use of e-diaries and on the neuroendocrine stress system by analysing hair cortisol. The multimodal assessment approach of symptoms, functioning, daily living outcomes, context variables and neuroendocrine effects, as well as the follow-up assessment, will enable us to analyse immediate and intermediate treatment effects not only on the phenomenological clinical level but also on the biological and daily living level. This will extend our understanding of intervention effects, influencing factors and the course of trauma-related mental health problems in refugee minors.

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Reporting checklist for protocol of a clinical trial.

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

		Reporting Item	Page Number
Administrative information			
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	3
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	3
Protocol version	#3	Date and version identifier	6
Funding	#4	Sources and types of financial, material, and other support	21
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	1, 21
Roles and responsibilities: sponsor contact information	#5b	Name and contact information for the trial sponsor	21
Roles and responsibilities: sponsor and funder	#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	21

Roles and responsibilities: committees	#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)	7, 16ff
Introduction			
Background and rationale	#6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	4ff
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	---
Objectives	#7	Specific objectives or hypotheses	5,6
Trial design	#8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory)	7
Methods: Participants, interventions, and outcomes			
Study setting	#9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	7 Reference: DRKS00020771
Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	8,16

Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	11ff., table 2
Interventions: modifications	#11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease)	12
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	16
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	8
Outcomes	#12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	5,6, 13-16, 18ff, Figure 1, Table 1
Participant timeline	#13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	9-12, table 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	17,18
Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	8, 9
Methods: Assignment of interventions (for controlled trials)			

Allocation: sequence generation	#16a	Method of generating the allocation sequence (eg, 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	9
Allocation concealment mechanism	#16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	9
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	9
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	7
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	----
Methods: Data collection, management, and analysis			
Data collection plan	#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	9, 13ff, 16ff Table1 Additional table2
Data collection plan: retention	#18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be	8

		collected for participants who discontinue or deviate from intervention protocols	
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	16ff
Statistics: outcomes	#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	17ff
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	17ff
Statistics: analysis population and missing data	#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)	18
Methods: Monitoring			
Data monitoring: formal committee	#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	16
Data monitoring: interim analysis	#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	7
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	9, 10, 12 table 1

Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	16
Ethics and dissemination			
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	19
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)	19
Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	9
Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in studies, if applicable	15,16
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	17
Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	21
Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	17
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	8, 9
Dissemination policy: trial results	#31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication,	19

		reporting in results databases, or other data sharing arrangements), including any publication restrictions	
Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	--
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	--
Appendices			
Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	Additional document
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	--

Psychometric instruments

If not available psychometric properties for internal consistency and reliability, criterion validity and convergent validity will be calculated within our sample.

Inclusion and exclusion criteria

Essen Trauma Inventory for Children and Adolescents

The Essen Trauma Inventory for Children and Adolescents (ETI-CA; (1, 2)) comprises a list of traumatic events and assesses symptoms of acute adjustment disorder and PTSD according to DSM-IV criteria (3) within the last four weeks, in relation to the most disturbing traumatic event if more than one was experienced. It further assesses the degree of impairment in six areas of daily living (e.g., school, peers) due to the traumatic event. It is available as a self-report questionnaire and an interview version, with the latter being used in this study. ETI-CA has been designed for the age group 12-17 years and is available in German and English. If necessary, we will translate the ETI-CA interview into Arabic, Dari, and Somali.

Clinical Global Impression Scale – Severity of illness

The Clinical Global Impression Scale is an internationally used instrument and yields the three different measures: 1. Severity of illness (CGI-S), 2. Global improvement (CGI-I), and 3. Efficacy index (4). In our study, we will apply the CGI-S, which is a 7-point scale on which the clinician rates the severity of the patient's illness at the time of assessment relative to the clinician's past experience with patients with the same diagnosis. Possible ratings range from 1=not ill at all to 7=among the most extremely ill patients. The German version of the scale (4) is clinically rated by study staff.

Kiddie-Schedule for Affective Disorders and Schizophrenia, Present and Lifetime

The Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime version (K-SADS-PL) is a widely used, validated, semi-structured diagnostic interview for the standardized assessment of mental disorders according to DSM-5 in children and adolescents aged 6-18 years (5-7). For the purpose of this study we will use the K-SASDS-PL diagnostic screening interview with subsequent diagnostic interviews if indicated, and the summary lifetime diagnosis checklist. The diagnostic screening interview reviews the most severe current and past major symptoms of all diagnoses assessed with the K-SADS-PL. If the participant displays indicative symptoms of a specific disorder according to the screening, the referring diagnostic interviews will be applied. The K-SADS-PL comprises the following diagnostic interviews: depressive and bipolar-related disorders, psychotic disorders, anxiety disorders, obsessive-compulsive disorders, trauma-related disorders including PTSD, externalizing disorders, eating disorders, and substance abuse disorders. The summary lifetime diagnosis checklist then summarizes all mental diagnoses assessed by the K-SADS-PL. The K-SADS-PL is available in German and English for the purpose of the study If needed, the interview is conducted with the assistance of an interpreter.

Alcohol Use Disorders Identification Test

The Alcohol Use Disorders Identification Test (AUDIT) is an internationally used, validated, self-report questionnaire approved by the World Health Organization to screen individuals for hazardous or harmful alcohol consumption and alcohol dependence. It can be applied from age 14 years onwards. Items are rated on a 5-point Likert scale (0-4). Total possible AUDIT scores range from 0-40. Scores of 8-10 or more are indicative of hazardous, harmful alcohol use or possible alcohol dependence. The AUDIT is freely available in many languages, including Arabic,

English and German (8). For the purpose of our study, we translated the questionnaire into Dari and Somali.

Columbia-Suicide Severity Rating Scale

The Columbia-Suicide Severity Rating Scale (C-SSRS) assesses suicidal ideation and behavior. Questions are phrased for use in an interview format. The C-SSRS measures the following constructs: severity of suicidal ideation, intensity of suicidal ideation, suicidal and/or self-harm behavior, and lethality of suicide attempts. It is provided in a lifetime and recent/since last visit version (9). We use the lifetime version for the first assessment at the screening visit and the recent/since last visit version for all other study visits. In addition to the original validated English version, the C-SSRS is available in a German version and has been translated into Arabic, Dari, and Somali.

Test of Nonverbal Intelligence, fourth edition

The Test of Nonverbal Intelligence, Fourth Edition (TONI 4) is a language-free, validated intelligence test that requires no reading, writing or speaking on the examinee's part. It can be used from the age of six years onwards. Test items present a variety of problem-solving tasks in ascending order of difficulty. The abstract, figural content of the test items reduces the cultural loading of the test and the result is not influenced by insufficient language skills (10).

Questionnaire to Assess Endangerment to Others

The standardized Questionnaire to Assess Endangerment to Others is a self-designed, self-rated questionnaire in accordance with the wording of the C-SSRS (9), which assesses thoughts or behaviors within the last six months displaying endangerment or threat to others. The questionnaire comprises six questions that are answered in a yes/no structure and is provided in Arabic, Dari, English, German and Somali.

Primary endpoints

Perceived Stress Scale, 10-item version

The Perceived Stress Scale, 10-item version (PSS-10), is a validated self-report questionnaire that assesses psychological distress during the preceding month. It measures the intensity with which individuals appraise their daily life as stressful, unpredictable, uncontrollable, and overloaded. The PSS-10 was designed for use in participants aged 14 years or older. Items are rated on a 6-point scale from 0=never to 5=often. In addition to the original English version (11), a validated German version (12) and an Arabic version are available (13). For the purpose of this study, we translated the PSS-10 into Dari and Somali.

Impact of Event Scale-Revised

The Impact of Event Scale-Revised (IES-R) is a validated, self-report questionnaire assessing traumatic symptoms on three subscales: intrusion (intrusive thoughts, nightmares, intrusive feelings and imagery, dissociative-like re-experiencing), avoidance (numbing of responsiveness, avoidance of feelings, situations and ideas), hyperarousal (anger, irritability, hypervigilance, difficulty concentrating, heightened startle), and an overall measure of traumatic distress. Items are rated on a 5-point Likert scale from 0=not at all to 4=extreme. In addition to the original English version (14, 15), a validated German version (16) and an Arabic version (17) are available. For the purpose of this study, we translated the IES-R into Dari and Somali.

Secondary endpoints

Trauma symptoms

Child and Adolescent Trauma Screen-2

The Child and Adolescent Trauma Screen-2 (CATS-2) is a validated, freely accessible self-report questionnaire based on the DSM-5 PTSD criteria. It assesses DSM-5

criteria A (experience of a traumatic event ever), B (intrusion, re-experiencing), C (avoidance), D (negative alterations in cognitions and mood), and E (hyperarousal). Criteria B-D are rated on a 4-point scale (0=never, 3=almost always). Trauma-related psychosocial impairment (peers, family, school/work, hobbies, well-being) is assessed with yes/no items. For the purpose of this study, we use the validated English and German CATS-2 self-report versions (18) and translated the scale into Arabic, Dari and Somali.

Posttraumatic Cognitions Inventory - child version

The Posttraumatic Cognitions Inventory - child version (cPTCI) is a validated, self-report questionnaire assessing trauma-related cognitions on the subscales 'permanent and disturbing change', 'fragile person in a scary world' and on an overall score. Items are rated on a 5-point Likert-type scale and are summed to form a total score and the two subscales scores. For the purpose of this study, we use the validated English version (19), a validated German (20) and an Arabic cPTCI version (21) and translated the cPTCI into Dari and Somali.

Disturbing Dream and Nightmare Severity Index

The Disturbing Dream and Nightmare Severity Index (DDNSI) is a validated, self-report questionnaire and assesses number of nights with nightmares per week (0-7 nights), total number of nightmares per week, severity of nightmares, intensity of nightmares (Likert-type scale: 0=no problem to 6=extremely severe problem), how often nightmares result in awakenings (0=never/rarely to 4=always). The scale provides five sub-scores and a total score (22, 23). For the purpose of this study, the DDNSI was translated into Arabic, Dari, German, and Somali.

Emotion Regulation

Difficulties in Emotion Regulation Scale

The 18-item version of the Difficulties in Emotion Regulation Scale (DERS-18; (24)) is a validated, self-report questionnaire assessing the following six components of emotion dysregulation on a 5-point Likert-type scale: 1) Nonacceptance of emotional responses, 2) Difficulties engaging in goal-directed behavior, 3) Impulse control difficulties, 4) Lack of emotional awareness, 5) Limited access to emotion regulation strategies, 6) Lack of emotional clarity. It can be used from the age of 13 years onwards and yields a total score as well as subscale scores. For the purpose of the study, we use the 18 items from the unpublished German validation study of the DERS-36 (25, 26) and translated the English version of the DERS-18 (24) into Arabic, Dari and Somali.

General Psychopathology

Strengths and Difficulties Questionnaire

The Strengths and Difficulties Questionnaire (SDQ) is a widely used, validated parent-/caregiver-rated and/or self-report screening questionnaire for children and adolescents that is freely available online in an English version (27), German version (28), Arabic version (29), and Somali parent/caregiver version (30). The SDQ screens for difficulties in four areas: 1) emotional symptoms, 2) conduct problems, 3) hyperactivity/inattention, and 4) peer relationship problems. It additionally assesses strengths in prosocial behavior and provides a total score that sums up all subscale scores. For the purpose of this study, we use the available Arabic, English, German, self-report, and caregiver SDQ as well as the Somali caregiver version, and translated the SDQ caregiver and self-report version into Dari and the self-report version into Somali.

Beck Depression Inventory, second edition

The Beck Depression Inventory, second edition (BDI-II) is a widely used, validated, self-report questionnaire that assesses the severity of depression according to DSM-

IV criteria on a 4-point Likert-like scale. It can be used in adolescents from age 13 years onwards. The BDI-II is available in a validated English (31), validated German (32) and a validated Arabic version (33), which we use in this study as well as a translated Dari and Somali version

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