RE-DEFINE:

Refugee Emergency: DEFining and Implementing Novel Evidence-based psychosocial interventions

Study protocol for review by WHO Ethical Review Committee.

Turkey

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Version 4.1

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PROJECT SUMMARY

Background

Since the start of the war in Syria in 2011, more than 5 million Syrians had to take refuge in a safer place and they had chosen neighbouring countries including Turkey, Lebanon, Jordan, Iraq and countries in Africa including Egypt and North Africa (1). Along with displacement from their homes, refugees also have been susceptible to countless traumatic events and lack of vital needs during and after displacement (2). Physical and mental challenges they endure do not end after resettlement as well. As a consequence of aforementioned adversities, refugees are at great risk of developing symptoms of common mental disorders, notably posttraumatic stress disorder (PTSD), depression, anxiety and related somatic health symptoms along with other forms of disabling psychological distress (3;4;5;6;7). The World Health Organization (WHO) has developed a new low-intensity 5-session self-help intervention called Self-Help Plus (SH+) in order to manage stress and cope with adversity (8). SH+ is a brief and trans-diagnostic intervention which may be delivered by trained non-specialists facilitators to people with and without mental disorders. SH+ has been evaluated in RCTs in low and middle income countries, while there is no rigorous evidence on its cost-effectiveness in preventing the onset of mental disorders in refugees in Turkey.

Objectives

To evaluate the effectiveness and cost-effectiveness of SH+ in Arabic speaking people including Syrians under the temporary protection of Republic of Turkey and other Arabic speaking immigrants and asylum seekers with psychological distress resettled in Turkey, as compared with enhanced treatment as usual (ETAU). The primary outcome is the reduction in the incidence of any mental disorders. Secondary outcomes are mental health symptoms, psychological functioning, well-being, drop-out rates, and economic outcomes.

Design

This is a parallel-group randomized controlled trial, in which participants will have an equal probability (1:1) of being randomly allocated to the SH+ intervention or the ETAU.

Methodology

Arabic speaking people including Syrians under the temporary protection of Republic of Turkey and other Arabic speaking immigrants and asylum seekers who screen positive at the General Health Questionnaire (≥ 3) and without a formal diagnosis of any psychiatric disorders according to the M.I.N.I. International Neuropsychiatric Interview (M.I.N.I.) will enter the study. After random allocation they will receive the 5-session SH+ or the ETAU. Assessments will be performed by masked members of the research team immediately after intervention, at 6 months (primary outcome), and a 12 months after randomization.

Time frame

The recruitment phase will last 12 months. After the screening, eligible participants will be assessed at baseline before randomization, immediately post-intervention, and at 6- and 12-monthsfollow-up. The SH+ intervention delivery will be conducted in around 5 weeks (1 session per week).

Expected outcomes

The expected outcomes are a reduction in the incidence of psychiatric diagnoses at 6-month follow-up, and a general improvement in mental health symptoms, psychological functioning, well-being, and economic outcomes at each assessment, in refugees in the SH+ intervention arm, as compared to ETAU.

GENERAL INFORMATION

Project title:
RE-DEFINE: Refugee Emergency – DEFining and Implementing Novel Evidence-based psychosocial interventions

Name of the sponsor/funder:
European Commission, H2020-SC1-2016-2017, topic: SC1-HCO-07-2017, project ID: 779255. The study sponsor has no role in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication. The study sponsor had no ultimate authority over any of the listed activities.

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LIST OF ABBREVIATIONS

AAQ: Acceptance and Action Questioannaire

CONSORT: Consolidated Standards of Reporting Trials

CSSRI: Client Service Receipt Inventory

DGMM: T.C. İçişleri Bakanlığı Göç İdaresi Genel Müdürlüğü (Republic of Turkey Ministry of Interior Directorate General of Migration Management)

DMP: Data Management Plan

DPO: Data Protection Officer

DSM: Diagnostic and Statistical Manual of Mental Disorders

EAB: Ethics Advisory Board

EDC: Castor Electronic Data Capture

ETAU: Enhanced Treatment as Usual

EU: European Union

GHQ: General Health Questionnaire

HIC: High Income Country

ITT: Intention-to-treat

M.I.N.I.: Mini International Neuropsychiatric Interview

MOU: Memorandum of Understanding

NGO: Non-Governmental Organization

PCL: Post-Traumatic Stress Disorder Checklist

Checklist for DSM

PHQ: Patient Health Questionnaire

PM+: Problem Management Plus

PP: Per Protocol

PSYCHLOPS: Psychological Outcome Profile Instrument

PTSD: Post-Traumatic Stress Disorder

RAS: Refugees and Asylum Seekers

RCT: Randomized Controlled Trial

SH+: Self Help Plus

SOP: Standard Operating Procedure

UNHCR: United Nations High Commission for Refugees

WHO: World Health Organization

WHO CC: World Health Organization Collaborating Center

WHODAS: WHO Disability Assessment Schedule

RATIONALE AND BACKGROUND INFORMATION

Since the start of the war in Syria in 2011, more than 5 million Syrians had to take refuge in a safer place and they had chosen neighbouring countries including Turkey, Lebanon, Jordan, Iraq and countries in Africa including Egypt and North Africa (1). In the last years, the number of people who seek refugee status from European and bordering countries has gradually increased (9). As stated by the United Nations High Commission for Refugees (UNHCR), while there were only 8000 Syrians under temporary protection in Turkey by the end of 2011, Turkey hosts 3,635,841 registered Syrians under temporary protection as of the date of Februrary, 2019 (10;11). With more than 3 million Syrian refugees residing either in cities or refugee camps, Turkey hosts the highest number of refugees (12). Recent data do not demonstrate a decrease in the number of refugees in the short term, in fact, an increase is expected (13). In addition to that, there are 73.474 Arabic speaking people who applied to get international protection from Turkey in 2018 (65).

Along with displacement from their homes, refugees also have been susceptible to countless traumatic events such as death, threat of death, serious injury, torture, rape, death or disappearance of a loved one and lack of food, water and shelter either during or after displacement (7). Physical and mental challenges they endure do not end after resettlement since they are exposed to many stressors in host countries such as poverty, limited civil rights, unemployment, violence, oppression, burdensome adaptation process, social isolation, exploitation, early marriage or gender based-violence (14;15;16). When all of these adverse events are taken into consideration, it is clear that refugees are at great risk of developing symptoms of common mental disorders, notably posttraumatic stress disorder (PTSD), depression, anxiety and related somatic health symptoms along with other forms of disabling psychological distress (3;4;5;6;7).

There are many psychological interventions to treat mental health problems of refugees and these interventions have been demonstrated to reduce symptoms of psychological disorders including depression, anxiety and PTSD (17). Plenty of studies have been shown the effectiveness of treatment alternatives such as narrative exposure therapy (NET), eye movement desensitization and reprocessing (EMDR), and trauma-focused cognitive–behavioural therapy (TF-CBT) on refugee population (18;19;20;21;22). But there are several obstacles along the way of providing psychological interventions to refugees including insufficient numbers of mental health care professionals, language barriers, complex and long treatments, lack of focus on prevention strategies, lack of focus on increasing psychological functioning and well-being (3;23;24).

The World Health Organization (WHO) has developed a new low-intensity 5-session self-help intervention called Self-Help Plus (SH+) in order to manage stress and cope with adversity such as chronic poverty, displacement, gender-based violence and long-term armed conflict (8). SH+ is a brief and trans-diagnostic (i.e., addresses depressed mood, post-traumatic stress, other stress reactions and client-defined psychosocial problems) intervention which may be delivered by trained non-specialists facilitators to people with and without mental disorders. This intervention does not only aim to help people in coping with adversity but also increasing their psychological functioning and well-being. Small pilot studies without a control group have been conducted in order to investigate feasibleness of SH+ with South Sudanese refugees in Northern Uganda and Syrian people in Syria and South Turkey. The aims of the studies were to investigate feasibility and acceptability of the programme and to identify any further adaptations required prior to further effectiveness testing in a large cluster randomized controlled trial (recently successfully completed with positive results in Uganda). Against this background, this study will test the effectiveness of SH+ in reducing the incidence of common mental disorders (i.e. depression, anxiety, PTSD) and improving psychological functioning, mental health symptoms among Arabic speaking people including Syrians under the temporary protection of Republic of Turkey and other Arabic speaking immigrants and asylum seekers resettled in Turkey. Also, this study will evaluate the cost-effectiveness of SH+ in Turkey.

STUDY GOALS AND OBJECTIVES

Objectives

The objective of this parallel-group randomized controlled trial is to evaluate the effectiveness and cost-effectiveness of SH+ in refugees with psychological distress resettled in Turkey, as compared with enhanced treatment as usual (ETAU). The primary objective is testing the effectiveness of SH+ in reducing the incidence of any mental disorders. Secondary objectives are the evaluation of mental health symptoms, psychological functioning, well-being, drop-out rates, and economic outcomes.

Study hypotheses

1. SH+ intervention is superior to ETAU alone in lowering the incidence of any mental disorder at 6-month follow-up.

2. Refugees in the SH+ intervention arm will report an improvement in depression, anxiety and PTSD symptoms, psychosocial well-being and improved levels of psychological functioning, when compared to ETAU group.

3. Refugees in the SH+ intervention arm will incur lower health care costs compared to ETAU group.

STUDY DESIGN

RE-DEFINE in Turkey is a prospective, randomized, parallel-group trial that will follow study participants over a period of 12 months. Arabic speaking people including Syrians under the temporary protection of Republic of Turkey and other Arabic speaking immigrants and asylum seekers with psychological distress, but without a mental disorder according to the MINI International Neuropsychiatric Interview (M.I.N.I.) for DSM-V and ICD-10, will be randomly assigned to the SH+ intervention or to enhanced treatment as usual (ETAU). Participants, facilitators, and research staff involved in the screening and baseline assessment will not be blind to the interventions provided during the trial. Participants will be assessed at baseline before randomization, immediately post-intervention, and at 6 and 12-months of

follow-up (Appendix 6). All assessments carried out after random allocation will be performed by masked assessors. All phases of the trial will be recorded following the CONSORT statement (25;26).

METHODOLOGY

Eligibility Criteria

Inclusion criteria:

(a) Age 18 or above;
(b) Able to speak and understand Arabic
(c) Being an Arabic speaking person including Syrians under the temporary protection of Republic of Turkey and other Arabic speaking immigrants and asylum seekers;
(d) Presence of psychological distress, as shown by a score of 3 or more at the 12 item General Health Questionnaire (GHQ-12 $\geq$ 3);
(e) Both oral and written or online informed consent to enter the study.

Exclusion criteria:

(a) Presence of any mental disorders according to DSM-V and ICD-10, as shown by a positive M.I.N.I.;
(b) Acute medical conditions contraindicating study participation, based on clinical judgment of the trained interviewer who performs the screening;
(c) Clinical evidence of imminent suicide risk or suicide risk scored as "moderate or high" (or a positive suicidality behaviour disorder) by the M.I.N.I. (section SUICIDALITY);
(d) Clinical evidence that the decision-making capacity is impaired.

Box 1. *Definition of asylum seekers and refugees*

Syrians who fled to Turkey as a result of the humanitarian crisis in Syria are not considered as refugees or asylum seekers in Turkey, instead they are under temporary protection according to Law on Foreigners and International Protection, and the Temporary Protection Regulation. Because, Turkey signed the 1951 Geneva Convention with an additional condition. This condition involves a geographical limitation which only allows people who arrive from the west of Turkey to be liable to asylum procedures. Therefore, Syrians who seek international protection are not able to become refugees or asylum seekers in Turkey. The Directorate General for Migration Management (DGMM) is responsible for registration and verification of Syrians with regard to the Law on Foreigners and International Protection, and the Temporary Protection Regulation. Temporary protection allows Syrians to access public services (27). Throughout this protocol, Syrians under temporary protection may be referred as Syrian refugees in order to be in accordance with European study protocol of RE-DEFINE: SH+.

Setting

The study will be conducted in Turkey. A detailed description of the setting and the recruiting process is reported in Appendix 1. The recruitment strategy will be pragmatic and will involve local organizations, namely non-governmental organizations (NGOs), that are not only in Istanbul but in other cities of Turkey as well where refugees reside, and implement reception projects for refugees in Turkey. These non-governmental organizations should undertake integrated reception interventions that include food, housing, legal, educational, healthcare and social guidance and support, and the development of individual programmes to promote socioeconomic inclusion and integration. In the recruiting site, local organizations that comply with the criteria will be contacted and the RE-DEFINE project will be presented as a possibility

to screen refugees for psychological problems. Participant recruitment will occur in cooperation with one or more of these non-governmental organizations, depending on local context aspects (see Appendix 1). Refugees will be consecutively approached and invited to participate by members of the research team, in agreement with local service staff who will facilitate contacts. Research team members will be trained on how to conduct the interviews. The training on how to conduct interviews and collect data will be centralized and coordinated by UNIVR. Contacts with refugees will be conducted in comfortable and private locations which are convenient for the participant and safe for the staff and participants involved (Appendix 1).

Facilitators, interviewers and two research assistants are Arabic speaking people, therefore, cultural mediators are not required for this study.

All of the Arabic speaking interviewers will receive a specific training. This training will cover an

- Introduction to RE-DEFINE
- Aim of the survey
- Survey methods and materials of screening such as data collection forms and rating scales
- Principles of conducting an interview
- Questionnaires that will be used in the screening phase
- Wordings of the questions and examples
- Ethical issues, quality standards and ensuring capacity to consent
  Being sensitive to respondents' needs
  Psychological first aid
  Role-playing (Active re-enactment of the interviews)

Each interviewer will complete one or two interviews as a part of their training before the data collection process begins. In addition, there will be regular meetings (e.g. supervision) during the research phase to provide further training and address any further questions or concerns raised by the researchers where necessary.

Participants

In accordance with migration situation of Turkey, Arabic speaking people including Syrians under the temporary protection of Republic of Turkey and other Arabic speaking immigrants and asylum seekers will be the target population in Turkey.

Informed consent for screening (Appendix 3)

Informed consent will follow a two-step procedure: first, potentially eligible refugees will be approached by a member of the research team for oral and written informed consent for screening. If the refugee screens positive, she/he will be invited member of the research team to participate in the randomized controlled trial and will be provided with full trial informed consent (see Informed consent for trial below). Illiterate participants will be asked witnessed oral consent and a thumbprint in lieu of a signature, in line with recommendations from WHO (28). The witness will not be a member of the research team.

Due to the high number of participants to be screened, some screening may occur remotely, for example over telephone or video conferencing. In these instances, the same procedures will be followed, but an online consent form with a link will be used to record consent. This will have the same information as the in person consent form. This link will contain informed consent

form along with an identification (id) number and, accepting and declining options. The link and an id number will be shared with potential participants and if they are willing to participate, they may choose the accepting option to indicate their consent. By this way, the participants will have time to read the informed consent form beforehand and by using id numbers, we will protect participants' personal information. An oral consent will be asked for at the beginning of the screening interview.

A member of the research team will assess whether or not the prospective participant has the capacity to reach this decision for himself/herself. The member of the research team will judge the quality of that decision and considers whether the participant has agreed or refused to participate on the basis of freedom of choice and absence of coercion and having general understanding of the research and its intentions.

Informed consent for trial (Appendices 4-5)
Before being enrolled in the trial, oral and written information about the study and its purpose will be provided by a member of the research team - who will be trained on how to deliver information on the study. A written or online informed consent document that comprises both information about the study and the consent form will be shared with participants. After reading the informed consent document, time will be given to make a decision about participation, emphasizing that the decision will not influence housing, resettlement, relocation procedures. Refugees who decide to participate will be asked to complete a written or online consent form. The participant's consent will be confirmed by the personally dated signature of the participant and by the personally dated signature of the person conducting the informed consent discussion. At post-intervention, and at 6- and 12- months of follow-up, the member of the research team that will perform the assessments will verbally reaffirm that no benefits related to housing, resettlement or relocation procedures are associated with the participation in this study. An SOP will be drafted prior to the start of data collection to operationalise the informed consent process outlined in this protocol.

During the informed consent procedures for screening and for the trial:
1. the member of the research team will avoid any kind of pressing attitude towards refugees to participate in the study;
2. the member of the research team will explicitly state that the participants will not receive any kind of compensation for their participation in the study but there will be a small reimbursement for their time and transportation cost;
3. the member of the research team will support refugees in reading and completing the consent form in case of difficulties, in order to assure the full understanding of the information provided. The member of the research team will actively verify that participants understand the information asking specific questions to be answered by participants reflecting back the crucial concepts with their own words, as recommended in the scientific literature (29).
The The Ethics Advisory Board (EAB) will support development of the informed consent SOP, and will receive regular updates about how informed consent procedures are being received by participants, providing additional input to assist countries in adjusting procedures where necessary, as reported in the Memorandum of Understanding (MOU) (see Appendix 2).
Eligible refugees giving oral and written or online consent to participate will be asked to complete a baseline assessment (see below) and will be subsequently randomly allocated to SH+ or ETAU.

A member of the research team will assess whether or not the prospective participant has the capacity to reach this decision for himself/herself. The member of the research team will judge the quality of that decision and considers whether the participant has agreed or refused to

participate on the basis of freedom of choice and absence of coercion and having general understanding of the research and its intentions.

Screening phase

Arabic speaking people including Syrians under the temporary protection and other Arabic speaking immigrants and asylum seekers Syrian refugees that are in contact with local organizations for receiving legal, social, or other types of support/facilities will be invited to participate. As social media is commonly used by refugees in Turkey, online groups (e.g. Facebook and WhatsApp) will be used to announce the study. Screening will be performed in person or by telephone/videoconferencing. Information regarding how the screening was conducted will be stated in the recruitment form. Regarding the required actions in case of adverse reactions that may occur during the screening, along with the PI, from the team, a psychiatrist who works in a state psychiatric hospital and a clinical psychologist will be accessible as well. Participants giving oral and written consent to participate will be initially assessed using the General Health Questionnaire-12 in order to select a population with clinically significant psychological distress (GHQ-12 $\geq$ 3). As second step, those with a GHQ-12 $\geq$ 3 will be assessed for the presence of a mental disorder by means of the M.I.N.I.. Only Syrian refugees with psychological distress, but without a mental disorder, will be invited to participate in the randomized study. In order to prevent contamination, only one person per family will be invited to participate in the study. The first person identified as a potential participant in the household will be invited. If more than one person in the household is selected at the same time, the person who will be invited to participate in the study will be selected randomly.

Following the screening phase, refugees eligible for the trial will be informed about further details and procedures of the study and will be invited to participate in the trial phase. For refugees who do not meet the eligibility criteria, reasons for study ineligibility will be verbally explained to them.

Refugees that are excluded because of a diagnosis of a mental disorder will be advised to seek professional treatment, and contacts with local mental health care services will be facilitated to provide them with adequate care satisfying minimal quality criteria, particularly in the presence of acute symptom or risk of suicide. Local mental health care services that have the capacity to assist refugees with a psychiatric diagnosis will be contacted (see Appendix 1 for details). Based on the specific clinical needs of refugees, the pathway of care will include:

- pharmacological treatment;
- psychological support and/or psychotherapy;
- psychosocial rehabilitation.

These interventions (that may include hospitalization) will be delivered to refugees by multidisciplinary teams within the mental health departments in Turkey.

The structured referral mechanism will work as follows:

1. Before starting the trial, a member of the research team will inform the local mental health department(s) and personnel of the NGO about the RE-DEFINE project, including methodology, inclusion/exclusion criteria, population group, and will ask the department to identify a reference person to be contacted in the referral process (name and phone number of the contact person);
2. Refugees receiving a diagnosis of a mental disorder during the screening phase will be referred to the contact person of the local mental health department(s) or the personnel of the NGO who takes part in the implementation. The member of the research team will actively facilitate patient's engagement with mental health services, by following up with the service and the participant.

3. The member of the research team will follow-up by contacting the reference person of the mental health department or the NGO personnel after 3-5 weeks from the first referral. However, she/he will have no responsibility that refugees actually follow the suggested clinical pathway, as is usual practice with mental health services Turkey.

The member of the research team will have no responsibility in checking that refugees actually follow the suggested clinical pathway. Psychiatric care costs will be covered in accordance with the local healthcare system. Given the limited services and transient nature of some refugees in Turkey, it will not be possible for the research team to always check if Syrian refugees actually follow the suggested clinical pathway. Local healthcare systems will cover psychiatric care costs. An SOP will define in detail how the referral to mental health care services will be conducted.

Trial phase

Pilot phase

Before starting the study we will conduct a preliminary pilot phase with 3-4 participants for each site. This phase will allow testing different aspects related to the delivery of the intervention and assessments, feasibility, and time, prior to the performance of the trial. Participants of the pilot study will not be included in the final sample size. However, they will receive the experimental condition, and a close monitoring of their psychological status through two psychological assessments (one at baseline, and one at the end of the intervention). These assessments will be composed of the same instruments that will be used in the fully-powered trial.

Trial phase assessment

Assessments will take place at screening, at baseline (before random allocation), post-intervention (0-1 week after intervention), and at 6- and 12- months after randomization. The assessments at 6- and 12- months will be performed in person or by telephone/ videoconferencing, to ensure the required rates of follow up. Telephone or online assessment and counselling has been used in a range of studies, with a critical review concluding that findings to date are positive and online counselling can have a similar impact and replicate the therapeutic conditions found in face-to-face encounters[1]. In addition, a previous study has shown that a mixture of online and telephone based assessments for inclusion in a remote writing based intervention for Post Traumatic Stress Disorder (PTSD) can be feasibly implemented with war traumatised individuals in Iraq[2]. This approach is continuing to be used widely (http://ilajnafsy.bzfo.de/portal/en/)

Together, these findings suggest that remote therapy and thus assessment can be safely and feasibly applied. The use of audio/video communication will be piloted and used should the pilot show that this can be done safely and feasibly. For the Turkey site, audio/video assessments may be used for both screening and assessments).

Methods of assessment will be recorded, and if necessary, accounted for in the analyses. See Appendix 8 for copies of all screening and outcome measures.

[1] Richards, D. and Viganó, N. (2013), Online Counseling: A Narrative and Critical Review of the Literature. J. Clin. Psychol., 69: 994–1011. doi:10.1002/jclp.21974

[2] Knaevelsrud C, Brand J, Lange A, Ruwaard J, Wagner B. Web-Based Psychotherapy for Posttraumatic Stress Disorder in War-Traumatized Arab Patients: Randomized Controlled Trial J Med Internet Res 2015;17(3):e71

At baseline, socio-demographic data including sex, age, country of origin, education, religion, marital status and work status will be collected using an ad-hoc form developed specifically for RE-DEFINE. The form will also collect information on education, housing, employment opportunities in Turkey (as measures to improve social integration). Information on the adverse life events and environmental stressors will be collected using the Harvard Trauma Questionnaire Part A (HTQ) (30) and the Post-Migration Living Difficulties (PMLD) and the Recovery Environment (31). We will administer the HTQ Part A (30), in which respondents are asked whether they have experienced each of the events, and a 17-item Checklist for Post-Migration Living Difficulties (PMLD) (31).

In addition, the following assessment scales will be administered (as reported in Table 1 below and Appendix 7 assessment schedule):
1. baseline: ad-hoc recruitment form, WHODAS 2.0, PHQ-9, WHO-5 Wellbeing index, PSYCHLOPS, HTQ Part A, PCL-5, EQ-5D-3L, and CSSRI-EU (adapted);
2. post-intervention: GHQ-12, M.I.N.I., WHODAS 2.0, PHQ-9, WHO-5 Wellbeing index, PSYCHLOPS, PMLD, and PCL-5;
3. 6-month follow-up: GHQ-12, M.I.N.I., WHODAS 2.0, PHQ-9, WHO-5 Wellbeing index, PSYCHLOPS, PMLD, PCL-5, EQ-5D-3L, and CSSRI-EU (adapted);
4. 12-month follow up: GHQ-12, M.I.N.I., WHODAS 2.0, PHQ-9, WHO-5 Wellbeing index, PSYCHLOPS, PMLD, PCL-5, EQ-5D-3L, and CSSRI-EU (adapted).

Table 1 Overview of measures that will be administered during the study

Concept	**Screening**	**Baseline**	**Post-intervention**	**6-month follow-up**	**12-month follow-up**
Mental Capacity	Mental capacity form	Mental capacity form	Mental capacity form	Mental capacity form	Mental capacity form
Psychological distress	GHQ-12		GHQ-12	GHQ-12	GHQ-12
Psychiatric diagnosis	M.I.N.I.		M.I.N.I.	M.I.N.I.	M.I.N.I.
Socio-demographic and migration data		Recruitment form			
Functioning		WHODAS 2.0 – interviewer administered	WHODAS 2.0 – interviewer administered	WHODAS 2.0 – interviewer administered	WHODAS 2.0 – interviewer administered
Depressive symptoms		PHQ-9	PHQ-9	PHQ-9	PHQ-9
Subjective wellbeing		WHO-5 Wellbeing index	WHO-5 Wellbeing index	WHO-5 Wellbeing index	WHO-5 Wellbeing index
Self-defined psychosocial goals		PSYCHLOPS	PSYCHLOPS	PSYCHLOPS	PSYCHLOPS

Traumatic/Adverse life events		HTQ –Part A/1			
Daily and Environmental Stressors			PMLD	PMLD	PMLD
Symptoms of PTSD		PCL-5	PCL-5	PCL-5	PCL-5
Health-related quality of life		EQ-5D-3L		EQ-5D-3L	EQ-5D-3L
Cost-effectiveness		CSSRI-EU		CSSRI-EU	CSSRI-EU

Primary outcome
The primary outcome will be the number of participants with a current psychiatric diagnosis at six-month follow-up, as measured by the M.I.N.I..

Psychiatric diagnosis at six-month follow-up
The M.I.N.I. was designed as a brief structured interview for the major psychiatric disorders (i.e., major depressive disorder, suicide behavior disorder, post-traumatic stress disorder, social anxiety disorder, etc) in DSM-5 and ICD-10. Validation and reliability studies have been done comparing the M.I.N.I. to the Structured Clinical Interview for DSM (Patient Edition) (32) and the Composite International Diagnostic Interview (33). The results of these studies show that the M.I.N.I. has similar reliability and validity properties, but can be administered in a much shorter period of time (mean 18.7 ± 11.6 min., median 15 min.) than the above-referenced instruments. It can be used by health care professionals with a clinical background, after a brief training session. Lay interviewers require more extensive training (34).

The M.I.N.I. is divided into modules identified by letters, each corresponding to a diagnostic category. At the beginning of each module (except for psychotic disorders module), screening question(s) corresponding to the main criteria of the disorder are presented in a gray box. At the end of each module, diagnostic box(es) permit(s) the health care professional to indicate whether the diagnostic criteria are met.

Secondary outcomes
Psychological distress (GHQ-12); number of participants with a psychiatric diagnosis at post-intervention and at 12-month follow-up (M.I.N.I.), functioning (WHODAS 2.0), depressive symptoms (PHQ-9), subjective wellbeing (WHO-5 Wellbeing Index), self-defined psychosocial goals (PSYCHLOPS), health related quality of life (EQ-5D-3L), symptoms of PTSD (PCL-5), drop-out rates due to any reason, cost-effectiveness (CSSRI-TR adapted).

Psychological distress
General Health Questionnaire-12 (GHQ-12) (35). The GHQ-12 is a measure of current mental health developed by Goldberg in the 1970s, and it has been extensively used in different settings and cultures (36-38). The questionnaire asks whether the respondent has experienced a particular symptom or behaviour recently. Each item is rated on a four-point Likert scale (less than usual, no more than usual, rather more than usual, or much more than usual); and gives a total score of 36 or 12 based on the GHQ version and on the selected scoring methods. The most common scoring methods are bi-modal (0-0-1-1) for screening and Likert scoring styles (0-1-2-3) for outcome evaluation.

Psychiatric diagnosis at post-intervention and at 12-month follow-up
The M.I.N.I. interview will be administered also at post-intervention and at 12-month follow-up, to evaluate the presence of any mental disorders.

Functioning
The WHO Disability Assessment Schedule 2.0 (WHODAS) interviewer-administered version (39;40). The WHODAS is a generic assessment instrument assessing health and disability (39). It is used across all diseases, including mental, neurological and substance use disorders. It is simple to administer and applicable across cultures. WHODAS covers six domains (cognition, mobility, self-care, getting along, life activities, and participation). It assesses difficulties people have across these domains during the last 30 days. Difficulties are scored as none, mild, moderate, severe, or extreme. We will use the 12-item interviewer-administered version. Data on socio-demographic information (sex, age, education, marital status and work status) will be collected through questions A1-A5 of the WHO-DAS, which will be administered first (39;40).

Depressive symptoms
Patient Health Questionnaire-9 (PHQ – 9) (41). The PHQ-9 is a 9-item instrument measuring the presence and severity of depression. Major depression is diagnosed if five or more of the nine depressive symptom criteria have been present at least "more than half the days" in the past two weeks, and one of the symptoms includes depressed mood or anhedonia. Other types of depression are diagnosed if two, three, or four depressive symptoms have been present at least "more than half the days" in the past two weeks, and one of the symptoms includes depressed mood or anhedonia. As a severity measure, the PHQ-9 score may range from 0 to 27, since each of the nine items can be scored from 0 (not at all) to 3 (nearly every day) (41). The PHQ has been validated for a wide range of cultural groups.

Subjective well-being
WHO-5 - Wellbeing Index (42;43). The WHO-5 Wellbeing Index is a 5-item questionnaire measuring current psychological wellbeing and quality of life, rather than psychopathology. Scores range from 0 to 25. The scale has demonstrated sensitivity to change in wellbeing and is available in numerous languages.

Self-defined psychosocial goals
The Psychological Outcome Profiles instrument (PSYCHLOPS). The PSYCHLOPS consists of four questions (44). It contains three domains: problems (2 questions), function (1 question) and wellbeing (1 question). Participants are asked to give free text responses to the problem and function domains. Responses are scored on an ordinal six-point scale ranging from zero to five, producing a maximum score of 20. The pre- and post-therapy versions of PSYCHLOPS consist of the same four questions but the post-therapy version adds an overall evaluation question (determining self-rated outcome ranging from "much better" to "much worse"). PSYCHLOPS has been validated in primary care populations across several countries. It has been used in WHO mental health studies in Pakistan, Kenya, Lebanon and Uganda (Protocol IDs: RPC627; RPC656; RPC705).

Symptoms of PTSD
PTSD Checklist for DSM-5 (PCL-5). The PCL-5 is a 20-item self-report measure that assesses the 20 DSM-5 symptoms of PTSD. It takes approximately 5-10 minutes to complete. The PCL-5 can be scored in different ways: (a) a total symptom severity score (range - 0-80) can be obtained by summing the scores for each of the 20 items; (b) *DSM-5* symptom cluster severity scores can be obtained by summing the scores for the items within a given cluster, i.e., cluster B (items 1-5), cluster C (items 6-7), cluster D (items 8-14), and cluster E (items 15-20); (c) a

provisional PTSD diagnosis can be made by treating each item rated as 2 = "moderately" or higher as a symptom endorsed, then following the *DSM-5*diagnostic rule which requires at least: 1 B item (questions 1-5), 1 C item (questions 6-7), 2 D items (questions 8-14), 2 E items (questions 15-20); We will use an adapted version making reference to the past week instead of the past month, for sensitivity reasons.

Generic measure of health for clinical and economic appraisal
The EuroQol-5Dimension-3 level version (EQ-5D-3L). The EQ-5D-3L is applicable to a wide range of health conditions and treatments, it provides a simple descriptive profile and a single index value for health status that can be used in the clinical and economic evaluation of health care as well as in population health surveys (45). The 3-level version of EQ-5D (EQ-5D-3L) was introduced in 1990 by the EuroQol Group. The EQ-5D-3L essentially consists of 2 pages: the EQ-5D descriptive system and the EQ visual analogue scale (EQ VAS).
The EQ-5D-3L descriptive system comprises the following five dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Each dimension has 3 levels: no problems, some problems, and extreme problems. The patient is asked to indicate his/her health state by ticking the box next to the most appropriate statement in each of the five dimensions. This decision results into a 1-digit number that expresses the level selected for that dimension. The digits for the five dimensions can be combined into a 5-digit number that describes the patient's health state. The EQ VAS records the patient's self-rated health on a vertical visual analogue scale where the endpoints are labelled 'Best imaginable health state' and 'Worst imaginable health state'. The VAS can be used as a quantitative measure of health outcome that reflects the patient's own judgement.

Proportion of participants leaving the study early (dropouts)
Number of people leaving the study prematurely at any times, and reasons for discontinuation. If possible, this information will be collected in person, or by telephone or secure online audio/video communication (two attempts will be made to reach participants). Unreachability of participants will also be recorded as a dropout.

Cost-effectiveness measures
The Client Service Receipt Inventory (CSSRI): Client sociodemographic and service receipt inventory (adapted version with other socio-demographic characteristics). The CSSRI is a research tool developed for collecting information that describes in detail the types and level of services that comprise the care package of each study member (46). These data are important in their own right as they can inform decisions about planning, commissioning and providing services to meet the needs of particular populations. However, the schedule is designed so that service use data are recorded in a standardized way that best facilitates the estimation of the component and total costs of support for each client. Just as needs or outcome data are collected at the individual level, in an economic evaluation it is important to measure the costs of the resources used to generate those outcomes for each client. The CSSRI is a questionnaire which takes approximately 20 minutes to complete and collects retrospective information about the interviewee's use of health and social care services, accommodation and living situations, income, employment and benefits. The CSSRI-EU is a European version of the CSRI. The CSSRI-EU was developed within the framework of the EPSILON (European Psychiatric Services: Inputs Linked to Outcome Domains and Needs) project. It will be further adapted to include relevant information for Turkey. The instrument is applicable for use in interview with patients and/or key staff.

For the purposes of RE-DEFINE, the European version of the CSSRI will be adapted to be used with refugees. This will be completed by sending the questionnaire to experts and local providers for comments on the questionnaire.

Traumatic life events and adverse life events
Traumatic/adverse life events and daily and environmental stressors will be collected by administering the HTQ-Part A and the 17-item Checklist for Post-Migration Living Difficulties (PMLD).
The HTQ, developed by Mollica and colleagues is a self-report questionnaire with 4 parts. The purpose of part 1/A is to measure traumatic life events.

The PMLD checklist was used to assess the levels of stress due to typical post-migration stressors developed from discussions with immigrant and refugee communities in Sydney. The checklist asks respondents to rate their experience of the problems, during the last 12 months, on a five point scale ('was not a problem' to 'a very serious problem'). A high cumulative score indicates a high degree of post-migration stressors.

Randomization
Randomization will occur at individual level and will be stratified by recruiting centre. Randomization will be centralized and coordinated by the WHO Collaborating Centre (CC) of the University of Verona. Eligible participants will be randomly assigned to one of the two groups with an equal probability of assignment to each group (allocation ratio 1:1). The randomization schedule will be generated using the web-based software Castor Electronic Data Capture (47). This electronic tool employs a variable block randomization method, in order to allocate groups randomly permuted in blocks of unequal size. The site investigator will not know the block size. Members of the research team involved in the recruitment will be able to access the web-based software to randomize each new enrolled participant, but will not be able to access the randomization list. In addition, the web-based software will allow random allocation only after the main information on the enrolled participant is entered, upon verification of the inclusion criteria. After random allocation, the software will produce a unique identification number (ID) for each participant. Recruiting members of the research team will be able to access the web-based software to randomize each new enrolled participant and will be immediately informed about the allocation arm, but will not be able to access the randomization list. The randomization list will be accessible only to the data manager.

There is a theoretical possibility of contamination by recruiting refugees who might interact with each other and therefore divulgate intervention's components from people in the experimental arm to those in the control condition. In order to minimize the possibility of any form of contamination, both the experimental and the control group will be asked to refrain from sharing study-related information and materials during the study. At all possible times during the trial, steps will be taken to organize the delivery of the intervention in a way that will prevent potential contamination.

Masking
Masking participants and facilitators about the intervention status will be impossible, due to the characteristics of the intervention. However, investigators evaluating primary and secondary outcomes post-intervention and at 6- and 12- months of follow-up, and the statistician performing all analyses, will be masked to the allocation status of the participants. Masking will be safeguarded, as interviewers involved in the assessments will be instructed on how follow-up assessments should be conducted in order to preserve effective masking. Similarly, the statistician analysing data will be allowed only to access encrypted data, where the nature of the intervention will be concealed.

In addition, to preserve masking:

1. we will ask the members of the research team to avoid interaction with study participants outside the study setting;
2. we will check that NGOs will provide appropriate private spaces for intervention's delivery and for the assessments.

Sample size and power calculations

On the basis of data extrapolated from prevention trials, it is expected an event rate (psychiatric diagnosis) of around 15% at six months (primary outcome) (48;49). However, these prevention trials were conducted in unselected populations that were not exposed to migration stressors. By contrast, refugees are exposed to pre-migration, migration and post-migration chronic stressors that are associated with up to ten times increased rates of mental disorders (50). On these grounds, we anticipate an incidence rate of mental disorders of 25% at six months in this population. It is hypothesized that the provision of the SH+ programme will show a clinically significant advantage by producing a between groups absolute difference of 10%. A sample size of 500 participants (250 in each group), achieves 80% power for a 0.05 level of significance between the two proportions of people diagnosed with mental disorders at six months. Assuming that a relevant proportion of refugees might be lost at study endpoint (due to the specific characteristics of this population), the final sample size will be of 600 participants (300 in each group). All trial phases will be piloted before the fully powered randomized trial with approximately 3-4 refugees in order to check and harmonise all procedures.

Characteristics of the experimental intervention

The Self Help Plus (SH+) programme

SH+ programme has been developed by WHO and collaborators working in the humanitarian field, with expertise in global mental health and psychosocial interventions. SH+ programme consists of a pre-recorded audio course, complemented with bibliotherapy, and thanks to this format not requiring much time from experts for implementation. The potential of using a psychoeducational course to access hard-to-reach populations has been demonstrated previously (51). Evidence for bibliotherapy is also promising (52). Furthermore, research has found that guided self-help programs produce much better results than "pure" (unguided) self-help, and the effects produced by guided self-help are surprisingly similar to face-to-face psychological treatment (53). SH+ was designed to be relevant for large segments of adversity-affected populations: it is intended to be transdiagnostic, easily adaptable to different cultures and languages, and both meaningful and safe for people with and without mental disorders. WHO organized extensive peer-review, with 43 international experts reviewing the intervention.

SH+ programme has two components: a pre-recorded course and a self-help book. Pre-recorded audio material (locally adapted) is delivered across five 2-hour sessions and in groups of 10 to 40 people. In order to be in accordance with the cultural norms and the preferences of target community, single gender groups will take place. The audio material imparts key information about stress management and guides participants through individual exercises and small group discussions. A written facilitator guide helps briefly trained non-specialist facilitators to conduct the course using these audio materials. To augment the course materials, an illustrated self-help book reviews all essential content and concepts. The book contains more than 400 illustrations and conveys key points with minimal text. It was written to be useful both as a standalone product and as a key resource for those participating in the course (8).
The format of SH+ is innovative in that it seeks to ensure that key intervention components are delivered as intended through the use of pre-recorded audio, without the burden of extensive training and supervision.

SH+ programme is based on acceptance and commitment therapy (ACT), a form of cognitive-behavioral therapy, with distinct features (54). ACT is based on the concept that ongoing attempts to suppress unwanted thoughts and feelings can paradoxically make these problems worse. Instead, it emphasizes learning new ways to accommodate difficult thoughts and feelings – primarily through mindfulness approaches – without letting them dominate, while guiding people to take proactive steps towards living in a way that is consistent with their values. ACT has been shown to be useful for a range of mental health issues (55) and has been used successfully in a guided self-help format (56). More specifically, SH+ includes ACT techniques that aim to reduce stress, live in accordance with ones values and to increase social support.

Delivery of SH+

The low -intensity SH+ programme will be delivered by trained non-specialist facilitators. Non-specialist SH+ providers, namely facilitators and co-facilitators will be refugees or community members with a refugee or migrant background or with the same/similar culture. They will have some prior experience in health or social or community work or volunteering. SH+ trainers will be local mental health care professionals that are affiliated with primary health care centres, community centres, or refugee mental health care or universities. Before starting the recruitment period, the SH+ trainers will receive specific training and supervision on the SH+ intervention from WHO.

SH+ is already available in Arabic and has been adapted and piloted extensively with Syrian people. The generic English version is translated to the relevant language with close attention paid to the form of language (e.g. colloquial) and tone (e.g. warm and caring) so it suitable for a psychological intervention. The book and a draft audio version are then reviewed by native speakers of the language. WHO and the translation teams then make further adaptations where necessary. This phase is repeated if required until both the language and the tone, voice and accent of the recording are deemed suitable. Finally the intervention is professionally audio recorded with a final review before use.

Characteristics of the control intervention

Enhanced Treatment as Usual (ETAU)

Control arm participants will receive routine social support and/or care according to ordinary practice and following local regulations. Additionally, they will receive baseline and follow-up assessments according to the study schedule, and information about freely available mental health services, social services and community networks providing support to people under temporary protection of Turkey and refugees, and NGOs' contact details. A member of the research team will preliminary inform local NGOs and community networks about this trial. The follow-up assessments will consist of interviews with members of the research team, and imply the creation of a supportive environment and a regular clinical assessment and the possibility of interacting with local NGOs' for receiving information on any issues related to social integration and support. However, as the control arm will include only participants without a psychiatric diagnosis, they will not be connected with mental health services, in order to avoid medicalization of their condition of psychological distress. In case some participants in the control group develop a mental health condition during the study, they will be connected with mental health services (as reported above).. In comparison, refugees that are excluded because of a diagnosis of a mental disorder will be actively connected to professional treatment and contacts with local mental health care services which will be facilitated by members of the research team (as reported above).

In this trial, in agreement with the regulations in Turkey, study participants will receive the same interventions provided to the local general population with the same psychological condition. People from the general population who are experiencing emotional distress but do not meet criteria for a diagnosis of mental disorder are usually provided with information on how to access health care services, including primary health care services and emergency services. Additionally, they are also referred to social support services, including social care facilities, charities, NGOs and other community resources. The NGOs that will take part in this study by referring potential participants from their beneficiries and providing logistic support will provide both informal and psychosocial support to the participants in the ETAU group. All these interventions will be offered to study participants at baseline and at each follow-up visit.
By contrast, for individuals with a mental disorder guidelines generally state they should receive health services. The above approach is consistent with these guidelines as it provides a) referral to services where a mental disorder is indicated at baseline (e.g. excluded from trial), b) information on available health services and support services (e.g. NGOs) for individuals accepted into the trial (distress but no mental disorder), c) ongoing assessment and referral to services for individuals in the trial who later develop a mental disorder.

SAFETY CONSIDERATIONS AND FOLLOW UP

Adverse events reporting
Serious adverse events and other adverse events reported spontaneously by the participants or observed by research or intervention staff will be recorded in a form specifically developed for adverse events reporting (see example form in Appendix 9). Data on the relationship with the study intervention, the action taken regarding intervention and the outcome of the adverse event will be collected.

An event is considered a potential adverse reaction if it is an undesirable experience occurring to a participant during the study, whether or not considered related to the research procedure. This definition includes all aspects of mental health and psychological functioning, but also any undesirable experiences. The chair or a nominated person from the Ethics Advisory Board (EAB - see Appendix 2) will review spontaneously reported serious adverse reactions (i.e., suicide attempts) within 48h, deciding if it is likely related or unrelated to the intervention. General adverse reactions will be reviewed by the EAB in regular bi-monthly meetings. In both instances, the EAB will determine if any appropriate action in respect of ongoing trial conduct is necessary and specify what action this would be (i.e. referral to specialized care). The site Principal Investigator will be responsible for ensuring that required actions are implemented. The site Principal Investigator will also inform trial participants and those bodies providing ethical oversight if anything occurs on the basis of which it appears that the disadvantages of participation may be significantly greater than was foreseen. SOPs will be prepared and followed for adverse events reporting.

Depending on the adverse event, follow up may require additional tests or medical procedures as indicated, and/or referral to a physician or specialist. All adverse events will be followed until care is in place for the client, or until a stable situation has been reached.

DATA MANAGEMENT AND STATISTICAL ANALYSIS

Data management

All study data will be managed with the electronic, web-based tool Castor Electronic Data Capture (EDC). This tool will allow to manage the entire study flow, including the collection of baseline assessments, the subsequent random allocation phase, the collection of socio-demographic and clinical data (including rating scales) and their storage in a dataset that will be used for statistical analysis.

A study administrator, based at the WHO CC of the University of Verona, will ensure the correct functioning of this electronic tool throughout the entire study course. The study administrator will not be involved in determining participants' eligibility, administering treatments, assessing outcome, or analysing data. The correctness and consistency of the data entered in the system will be ensured by an upstream validation of data entered, which provides an immediate feedback to the user entering data.

Castor EDC complies with all the most relevant national and international regulations to reliably and accurately design, conduct, monitor, record, analyse and report data of clinical trials, including Good Clinical Practice (GCP), 21 Code of Federal Regulation (CFR) Part 11, EU Annex 11, and the European Data Protection Directive. The validity of the application has been audited on the basis of the GCP/GAMP (61), and has been deemed qualified. In detail, this electronic tool fulfills all the following GCP data management requirements:

- An appropriate and consistent use of the system will be ensured by a set of SOPs.
- In order to ensure the confidentiality of records and safeguard the identity of participants, an unambiguous, anonymous and unalterable identification code will be automatically generated for each participant at the time of enrolment.
- In order to address the possibility of human errors altering the quality and consistency of the dataset, all entered data and all changes will be automatically saved throughout the study (audit trail, data trail and edit trail).
- A security system will be in place to prevent unauthorized access to data. Each researcher involved in the study will be allowed to access and use the web-based tool only to the extent that is related to their specific role (e.g. participants' recruitment, outcome assessment, data analysis, etc.). The study administrator, based in the WHO CC in Verona, will provide each researcher with specific rights for the use of the tool, preventing him/her to intentionally or unintentionally alter study data. The authorization to access data will be allowed only to those directly involved in the process of data analysis, for limited time periods.
- A list of all individuals authorized to make data changes will be kept. All alterations of user rights throughout the course of the study will be automatically recorded.
- All collected data will be automatically backed up and archived, so they can be easily retrieved at any time. As all data changes will be recorded, the status of a particular record at a particular moment in time can always be retrieved. Further, when data changes are made, an explicit motivation must be provided.
- The concealment of allocation will be safeguarded, as only users with randomization rights will randomize participants, without knowing in advance which group the participant will end up in. Also the masking will be safeguarded, as outcome assessors will be authorized only to collect and insert data in the system, but participant allocation to treatments will be concealed. Similarly, the statistician analysing data will be allowed only to access data with an encrypted information on the treatment allocation.
- The web-based system will comply with the FAIR Principles (Findable, Accessible, Interoperable, Reusable). In synthesis, collected data will be: (a) findable, as data will be organized and indexed in a searchable resource, and will be described with rich metadata. Further, data and metadata will be assigned a unique and unchangeable identifier; (b) accessible, as a standardized communications protocol

will be produced to allow retrieving data and metadata; (c) interoperable, as a formal, accessible, shared, and broadly applicable language for knowledge representation will be employed to name data and metadata; (d) reusable, as data and metadata will be identified by a plurality of accurate and relevant attributes.

In accordance with the Declaration of Helsinki (62), the participants' confidentiality will be preserved at all times and the contents of the recruitment and follow-up forms will not be disclosed to any third party.

Trial investigators will ensure that the trial is adequately monitored in order to ascertain the accuracy, completeness, and appropriateness of procedures employed to collect and register study data. Recruiting centres will allow the coordinating centre, at its discretion, to monitor and audit the conduct of any procedure related to the study. This includes the right to inspect any facility being used for the study and to examine any relevant procedure and record.
A Data Protection Officer (DPO) will supervise and regularly report that all data collection and processing is carried out according to EU and national legislations. The DPO will ensure compliance with requirements, will regularly monitor performance with the aim of addressing potential issues proactively. The DPO will keep all the data-relevant authorizations available and will produce periodic reports to accompany the periodic project reporting.

A Data Management Plan (DMP) including detailed information on the procedures that will be implemented for data collection, storage, protection, retention, merging, reuse and/or destruction will be drafted following the guidance issued by the European Commission (63). It will be drafted using a template (Version: 26 July 2016) provided by the European Commission, and will be updated over the course of the project whenever significant changes arise. The implementation of the DMP will be monitored by the EAB and the DPO.

According to the Guidance note on research on refugees and asylum seekers (64), a SOP for helping participants in case of incidental findings (human rights violations, human and sexual trafficking, domestic violence, forced marriage, female genital mutilation, trading in human organs, child pornography) will be drafted in order to ensure that the responsible national authorities, NGOs or other agencies with relevant expertise are informed following local legislation.

Statistical Analysis

General approach

The statistical analysis will be masked. The trial statistician will be blinded to the treatment groups until the analysis has been completed. Moreover, the trial statistician will not be involved in determining participants' eligibility, in administering the intervention, in measuring the outcomes, or in entering data (data will be entered with a double-entry procedure). All analyses will be performed using Stata/SE, Release 14.2.
Two data locks will occur during the study. The first one will happen 6 months after the end of the 12-month enrolment period (month 18 from study beginning), when the information on the primary outcome and on the short-term secondary outcomes will be available for all study participants. The second one will happen at the end of the study (month 24 from study beginning), when information on the long-term secondary outcomes will be available for all participants.
All primary and secondary analyses will be performed on an intention-to-treat (ITT) basis. The ITT population will consist of all participants randomly assigned to the competitive intervention strategies. In order to check the robustness of results, the primary outcome will be additionally analysed using a per protocol (PP) approach, that will include only participants who fulfil the protocol in terms of eligibility, interventions, outcomes assessment at follow-

ups. The analysis of the PP population will be used for confirmatory purposes only. If less than 5% of participants does not receive the allocated intervention according to the study protocol, the PP analysis will not be performed.

All analyses reaching statistical significance will be replicated for each recruiting centre and for each population group separately. In addition, all analyses reaching statistical significance will be stratified by methods of assessment (face to face versus telephone or secure online audio/video communication).

Analysis of the primary outcome

The proportion of participants with a psychiatric diagnosis at 6-months follow-up will be compared between the two groups through the chi-square test (primary analysis). A multivariate analysis (secondary analysis) will be performed through a Poisson regression model, with a robust error variance (57), to estimate relative risks directly and to explore the potential confounding effect of prognostic factors, and the interactions with treatment.

Analysis of the secondary outcomes

Secondary outcomes are:

- GHQ-12 post-intervention, at 6- and 12-months follow-up;
- Proportion of participants with a psychiatric diagnosis (M.I.N.I.) post-intervention and at 12 months of follow-up;
- WHODAS 2.0 post-intervention, at 6- and 12-months follow-up;
- PHQ-9 post-intervention, at 6 and 12 months of follow-up;
- WHO-5 Wellbeing index post-intervention, at 6 and 12 months of follow-up;
- PSYCHLOPS post-intervention, at 6 and 12 months of follow-up;
- EQ-5D-3L: at 6 and 12 months of follow-up;
- PCL-5 post-intervention, at 6 and 12 months of follow-up;
- CSSRI-EU (adapted) at 6 and 12 months of follow-up;
- Proportion of participants leaving the study early (dropouts).

Proportion of participants with a psychiatric diagnosis (M.I.N.I.) post-intervention and at 12 months of follow-up

The proportion of participants with a diagnosis of any mental disorder post-intervention and at 12-months of follow-up will be compared between the two groups through the chi-square test. A multivariate analysis will be performed through a Poisson regression model, with a robust error variance, to estimate relative risks directly and to explore the potential confounding effect of prognostic factors, and the interactions with treatment (57).

GHQ-12, WHODAS 2.0, PHQ-9, WHO-5 Wellbeing index, PSYCHLOPS, PCL-5 post-intervention, at 6- and 12- months of follow-up

For each questionnaire, in case of missing items, the Corrected Item Mean Substitution method (58), will be used (i.e. the item mean across participants weighted by the subject's mean of completed items), using information from subjects belonging to the same treatment arm for the same follow-up time.

The hypothesis that the experimental intervention has no effect on GHQ-12, WHODAS 2.0, PHQ-9, WHO-5 Wellbeing index, PSYCHLOPS, PCL-5 scores will be tested by performing seemingly unrelated regression (59), for each follow-up, controlling for baseline values. In case of joint statistical significance of the coefficients related to treatment status, the effect of treatment on each score will be evaluated through appropriate statistical methods for repeated measurements.

After the last data lock, a mixed analysis of covariance (ANCOVA) will be performed for each scale, using the values at post-intervention, and at 6- and 12- months of follow-up, controlling for the value at baseline. In case of joint statistical significance of the coefficients related to treatment status, the analysis for each outcome/time combination will be repeated using the last observation carried forward (LOCF) approach: ratings will be carried forward from the last available assessment to the 12-month follow-up assessment. Multivariate analyses will be performed for each scale to take confounding factors into account, again including the baseline value as a covariate.

Proportion of participants leaving the study early (dropouts)
The proportion of participants leaving the study early will be compared between the two groups through the chi-square test (or the Fisher exact test, where appropriate). A multivariate analysis will be performed through a Poisson regression model, with a robust error variance, to estimate relative risks directly and to explore the potential confounding effect of prognostic factors, and the interactions with treatment (57).

Cost-effectiveness analysis (CSSRI)
Overall incremental cost-effectiveness analyses (ICEA) will be conducted from the UK health and social care system perspective and from the UK societal perspective by means of the net-benefit approach (Glick, 2010). Direct costs including formal medical and psychiatric health care (inpatient care, outpatient care, staff, equipment, drugs; formal psychological), psychosocial care (psychological counselling, psychotherapy, social worker, community nurse, sheltered accommodation, day centre, occupational services), legal services (police and court contacts, arrests, legal guardianship), informal services (care provided by relatives or volunteers) will be used for ICEA from the health and social care system (payer) perspective and total (direct costs + productivity losses) will be used for ICEA from the societal perspective.
Comprehensive use of annual health and social care resources will be assessed by means of completing the adapted CSSRI-EU at baseline and at 6-month follow-up. Information on the unit-costs of the used services will be gained by the cost compilation for the UK health and social care system (Curtis & Burns, 2017). For services not listed in the UK compilation, price lists, fee charges, reimbursement claims and other sources will be used to identify unit costs. Costs of informal services provided by relatives or volunteers will be estimated on the basis of average salaries per hour. Total direct costs of service use will be calculated by multiplying service units with unit costs. Six months costs from the two surveys will be added to annual costs. Productivity losses will be estimated for asylum seekers and refugees with work permissions by means of the human capital approach (Brouwer & Koopmanschap, 1998) on the basis of group-specific average salaries. All costs will be calculated in 2017 UK £.
Total costs of health and social care use including costs of the SH+ implementation will be investigated with regard to the cost driving effects of asylum seekers and refugees characteristics and the impact of different levels of coverage, different macroeconomic, social and health care indicators by estimating regression based cost functions (Knapp, 1998).
Incremental cost-effectiveness ratios (ICER) will be calculated for the additional costs of gaining one quality-adjusted life year (QALY) by implementing SH+ compared to standard care. QALYs will be estimated on the basis of EQ-5D-3L using country specific utility scores (Szende, Janssen, & Cabases, 2014). The stochastic uncertainty of the ICER will be estimated by nonparametric bootstrapping with 2000 replications. Maximum willingness to pay necessary for a 95 % probability of the SH+ intervention to be cost-effective at a MWTP range between UK£ 0 and 50,000 will be estimated by means of the cost-effectiveness acceptability curve based on the net-monetary-benefit approach (Glick, 2010). Net-monetary benefit (NMB) for each participant will be computed as the QALY gain per patient (QALY) multiplied by the maximum willingness to pay (MWTP) for one QALY minus the direct or

total costs (C) per patient ($NMB_i = QALY_i*MWTP-C_i$) for a MWTP range between UK£ 0 and 50,000 in increments of UK£ 5,000 (Hoch et al., 2002). Incremental NMB will be computed by regressing the NMB on study group (Hoch, Briggs, & Willan, 2002). Results of ICEA will be interpreted according to UK MWTP thresholds recommended by the NICE (Appleby, 2016) and alternatively by country specific thresholds provided by (Woods, Revill, Sculpher, & Claxton, 2016).

Interim analyses
No interim analysis is planned for this trial.

Individual Participant Data meta-analysis
Anonymized Individual Participant Data (IPD) from this study will be re-analysed in an IPD meta-analysis collecting IPD from all available trials on SH+. An ad-hoc protocol for the IPD meta-analysis will be developed.
This secondary analysis of data (IPD meta-analysis) will be mentioned in the informed consent form for participants.

QUALITY ASSURANCE

Participants in the study may directly benefit from their participation in the SH+ intervention, which is based on AMBT techniques that are empirically supported. Their participation will furthermore inform adaptation of the SH+ manual into multiple languages, and thus improve knowledge about delivering mental health interventions in the study areas. Since SH+ is non-pharmacological and there is a broad evidence base for its use, it is unlikely that adverse effects due to the intervention will occur. Adverse events will be responded to as described above. The EAB will play a key role in monitoring adherence to the trial protocol and ensuring research quality as well as prompt and accurate reporting of adverse events.

EXPECTED OUTCOMES OF THE STUDY

The expected outcomes are a reduction in the incidence of psychiatric diagnoses at 6-month follow-up, and a general improvement in mental health symptoms, psychological functioning, well-being, and economic outcomes at each assessment, in refugees in the SH+ intervention arm, as compared to ETAU.

DISSEMINATION OF RESULTS AND PUBLICATION POLICY

A detailed dissemination and communication plan will be developed by WHO in collaboration with project partners. The plan will be circulated across the study sites for comments and final approval.

Local Community
Stakeholders in local communities will be informed about the research through liaison with key refugee and asylum seeker organisations. Further community consultations may be used when identified as necessary by the local research team. These might include meetings of experts and interested professionals or community leaders and community members.

Global mental health community
We will continue discussions with other agencies and research teams throughout this

project about SH+. Regular feedback and liaison will be maintained through existing coordination mechanisms for mental health services, which will increase the likelihood of implementation of SH+ following release.

Academic and Broader Dissemination
Academic articles will be drafted and submitted to leading journals with broad dissemination, with academic conference presentations given as well. Broad dissemination of WHO publications and tools tends to be excellent, especially in global mental health. On the basis of positive results from research trials of SH+, the package will be disseminated by WHO in multiple languages.

DURATION OF THE PROJECT

Activities	Month
Overall project management (coordinating the whole project, communicating with the EC, overseeing ethics approval and data management)	1-36
Preparatory work (including planning, training of SH+ trainers and facilitators)	1-6
Pilot and Trial Phase	
Pilot phase (recruitment of pilot participants, informed consent, screening and baseline assessment, randomization, implementation of ETAU and SH+, post-intervention assessment)	7-8
Recruitment of trial participants, informed consent, screening and baseline assessment, randomization	9-18
Implementation of ETAU and SH+	10-19
Post-intervention assessment	11-20
6-month follow-up	17-24
12-month follow-up	23-30
Statistical and cost effectiveness analyses	28-36

PROBLEMS ANTICIPATED

While challenges exist when doing research with populations affected by adversity and limited resources, the collaborators and their networks are experienced in mental health research and/or practice in their relevant settings. Collaborators have a good understanding of the local context and have relationships with relevant community organizations and NGOs, academic and healthcare services to ensure smooth running of this research and safety of participants. University of Verona have experience of coordinating international research, as well as extensive experience supporting refugees and asylum seekers in clinical services in Italy. The WHO team have experience of running trials in difficult situations (e.g. refugee settlements, conflict affected areas) and addressing common problems in RCTs. Both University of Verona and WHO will use this experience to support project partners through regular communication and coordination calls and meetings.

PROJECT MANAGEMENT

Professor Corrado Barbui of the University of Verona is the project coordinator and will be responsible for management of the overall project. WHO is responsible for training

and supporting sites in the use of the SH+ intervention. Dr. Ceren Acartürk will be responsible for implementing the study protocol locally. Please see Appendix 1 for a detailed description of the Turkey site.

ETHICS

It is essential to conduct this research because rigorous evidence needs to be collected on the effectiveness of this intervention, which has been specifically developed for vulnerable population groups. Additionally, it will provide valuable information about optimal adaptation strategies and aspects to consider when scaling up in another context.
The trial will be conducted according to globally accepted standards of good clinical practice (as defined in the ICH E6 Guideline for Good Clinical Practice, 1 May 1996), in agreement with the Declaration of Helsinki and in keeping with local regulations.

The following key ethical issues will be carefully taken into consideration:

- Ongoing monitoring of decision making capacity to consent to participate in the study. The decision making capacity will be evaluated using a specific form developed in accordance to the British Psychological Society guidelines for conducting research with people not having the capacity to consent to their participation. The form will be administered during the screening phase, at baseline, and at each follow-up assessment.
- Importance of robust referral mechanisms to mental health services.
- Monitoring of participants expectations from their involvement in the study (e.g. expecting this to affect their legal status). Moreover, members of the research team will clearly reaffirm that the participation in this study will not provide refugees with any benefits in terms of housing, resettlement or relocation procedures.
- Safety of members of the research team involved in the study, including, if required, gender matching and awareness of socio-demographic differences to participants and impact this may have on the research encounter.
- Intervention delivery: importance of gender matching.
- Facilitator training and supervision to ensure their competency to practice and protect against burnout / additional stress due to being exposed to participants experiences.

The participation in the study will be on a voluntary basis. During the informed consent procedures for screening and for the study this will be explicitly stated in written (in the informed consent form) and with oral communication by the interviewer.

An international EAB will supervise all the ethical issues related to the trial. Activities of the EAB are described in detail in a Memorandum of Understanding (Appendix 2). The EAB will help the consortium keep high ethical standards, which will ultimately enhance the quality of research, increase its likely social impact, promote integrity and a better alignment of RE-DEFINE with social needs and expectations. The EAB will make sure that relevant steps are undertaken to minimize risks or provide solutions in case relevant psychological problems are detected during screening or during the course of the study. The EAB will indirectly supervise three main aspects: (1) recruitment, inclusion and exclusion criteria, and informed consent procedures; (2) data management (protection and privacy); (3) vulnerability of the population.

Benefits and risks

Potential benefits

- Access to a new preventive psychosocial intervention, and receiving the intervention for free;

- Regular and careful attention to the psychological status during the study. Assessments from members of the research team will guarantee close monitoring of participants mental health;
- Benefits in terms of psychological symptoms and functioning, quality of relationships, and solutions of specific problems both related and unrelated to their traumatic experiences, breaking of unhealthy patterns, and a significant reduction in feelings of distress.
- Contributing to a research that may limit the incidence of newly diagnosed psychiatric disorders in refugees resettled in Turkey.

Potential risks

- There are no guarantees of what participants will experience, and of the duration of changes. For example, it could be that benefits won't last for long periods;
- Based on data from randomized controlled trials already testing the SH+ we are not expecting the intervention worsening mental health condition of participants. However, it could be that participants will experience a transient increase of their mental health problems. In order to mitigate these risks, follow-up assessments and networking with NGOs have been planned to closely monitor the psychological status of participants. In addition facilitators will be trained in basic helping skills and identification of serious adverse events (e.g. imminent risk of suicide) which will further aid identification of any adverse reactions to SH+. Facilitators will be regularly supervised by mental health professionals to further address this risk;
- Participants will not be able to choose in which study arm they will be allocated;
- Participants might experience uncomfortable feelings like sadness, guilt, anger, frustration, and loneliness. Approaching feelings that participants have tried to avoid for a short or long period of time may be painful;
- The participant burden related to the involvement in this study may compete with on-going responsibilities faced by newly re-settled people (i.e., housing, language issues, new medical system, etc.). This issue has been considered when planning study timeline and assessments. The study is pragmatic and participation implies only 4 assessments of 1 hour each. However, it will be taken into careful consideration throughout the course of the study;
- Participants might feel uncomfortable in a group setting.

INFORMED CONSENT FORMS

Three informed consent forms specific to Turkey have been prepared and attached:
1) one for screening (for the pilot or trial phase) (Appendix 3)
2) one for participation in the trial phase RCT (Appendix 4)
3) one for participation in the pilot (Appendix 5, with differences from Appendix 4 highlighted in green).

BUDGET

The budget has been uploaded (see Appendix 10).

This study has received funding by the European Union Horizon 2020 Research and Innovation Action (RIA), under grant agreement n. 779255. A budget table detailing study related costs have been produced agreed and signed by the involved sites in a Grant Agreement.

OTHER SUPPORT FOR THE PROJECT

None

COLLABORATION WITH OTHER SCIENTISTS OR RESEARCH INSTITUTIONS

The scientists collaborating in this project are all listed in the General Information section of this document and Appendix 1.

LINKS TO OTHER PROJECTS

This project is related to current WHO project trialing a related low-intensity intervention, including: *Problem Management Plus (PM+)*, where trials have been completed in Kenya and Pakistan (WHO Ethical Research Committee Protocol IDs: RPC627; RPC656; RPC705), Self Help Plus (SH+) in Uganda (RPC758) and Step by Step (ERC.0002797)

CURRICULUM VITAE OF INVESTIGATORS

These are attached.

OTHER RESEARCH ACTIVITIES OF THE INVESTIGATORS

Other research activities by the investigators are summarised in the attached CVs.

FINANCING AND INSURANCE

The implementing agency will ensure free of charge follow-up on any adverse events, or serious adverse events, caused by the study. Therefore, insurance is not deemed necessary.

LIST OF APPENDICES

Appendix 1. Description of Turkey Study Site

Appendix 2: Memorandum of Understanding – Activities of the Ethics Advisory Board for the RE-DEFINE Project

Appendix 3: Informed Consent Form for Screening (for both pilot and trial phase) (Turkey-specific version)

Appendix 4: Informed Consent Form for Participation in RCT (Turkey-specific version)

Appendix 5: Informed Consent Form for Participation in Pilot (Turkey-specific version)

Appendix 6: Study flow diagram

Appendix 7: Assessment Schedule

Appendix 8: Screening and Outcome Measures

Appendix 9: Example of Adverse Events Reporting Form

Appendix 10: Budget for RE-DEFINE

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