1. **Title**: Neurofeedback as a treatment for trauma-affected refugees - A pilot study

2. **Status of the project**: The project is currently recruiting participants.

3. **Project period**: 1.11.18-31.12.19

4. **Investigator(s)**: Erik Vindbjerg, Clinical psychologist and Sigrid Zeuthen Hannemose, medical student.

5. **Supervisors and collaborative partners**:
   Principal supervisor: Associate Professor Jessica Carlsson Lohmann, CTP.
   Collaborative partners: Søren Bo Andersen, PhD, Kasper Eskelund, PhD, the Department of Military Psychology Department, Danish Veteran Centre, Copenhagen.

6. **Background**:
   Randomized controlled trials on trauma-affected refugees carried out at the Competence Centre for Transcultural Psychiatry (CTP) point to limited treatment outcome with standard best practice PTSD treatment. A recent systematic review and meta-analysis on psychosocial interventions with trauma-affected refugees and asylum-seekers showed a rather small effect of interventions on PTSD. Thus, there is a need to explore alternative and adjunctive therapies to improve outcomes.

   Technology can assist individuals in learning to control their physiology by providing them with a real-time report of biological activity. As an example, training aimed at relaxing may rely on measures of heart rate and respiration. The participant will then receive continuous feedback, e.g. in the form of sound or graphics, to indicate if he or she is moving in the direction of a more relaxed state. This process, where feedback guides the participant in the direction of the desired biological activity, is generally termed *biofeedback*. A subfield of biofeedback utilizing electro-encephalography (EEG) to specifically target brainwave activity. This subfield is termed *neurofeedback*.

   In neurofeedback, the brainwave activity is fed back to the person as an auditory or visual signal, rewarding the person each time progress is made toward normalizing dysregulated neural activity. This may, as an example, imply movement from a state of hyperarousal towards calm alertness. The learning mechanism is at its base considered to be operant conditioning, where the behaviour of the participant—in this case, neurological activity—is gradually changed through repeated reinforcement. In neurofeedback, this simple learning mechanism is accelerated by continuous and instant feedback, with rewards occurring as often as every second.

   Neurofeedback has been particularly applied and evaluated in the treatment of attention deficit hyperactivity disorder (ADHD). It has proven highly effective for reducing inattentiveness and impulsivity. Neurofeedback is also showing promising results in the treatment of depression, anxiety, insomnia, autism, addictions, and PTSD. A recent review of the effect of neurofeedback in the treatment of PTSD found that neurofeedback training appears effective in alleviating symptoms, and demonstrates changes in patients brainwave activity as well as their fMRI connectivity of core neurocognitive networks. Recent studies also indicate that neurofeedback may be effective for patients with complex and chronic PTSD. A recent study by Gapen and colleagues was based on patients who typically suffered multiple traumas, displayed an early onset of PTSD symptoms, and who had seen no or little response to years of psychotherapy. Here, neurofeedback resulted in a medium to strong effect on PTSD symptoms (Cohens $d = 0.69$).
There are no published peer-reviewed studies testing the outcome of neurofeedback with refugees. However, small pilot studies have been carried out by clinicians in two settings: the Swedish Red Cross Center for Victims of Torture and War in Malmö, Sweden, and the NSW Service for the Treatment and Rehabilitation of Torture and Trauma Survivors (STARTTS) in Sydney, Australia. Results of the former have been published in a dissertation\textsuperscript{8}, while the latter has been reported in a training program at STARTTS, in which both the sponsor, Jessica Carlsson Lohmann, and investigator, Erik Vindbjerg, have participated. Both evaluations show very favourable results with a remarkable drop in PTSD symptom severity. The corresponding effect sizes, as indicated by Cohen’s $d$, were in the range of 1.0 – 2.2.

7. Aim/s
This study is based on the hypothesis that the positive effects of NF demonstrated in other traumatized populations also apply to refugees.

The study has three objectives:
- To assess the recruitment and retention rate in a diverse sample of refugees offered neurofeedback as an adjunct therapy.
- To assess patients' perceived satisfaction as well as potential discomfort related to the neurofeedback intervention.
- To measure changes in symptoms during treatment in order to evaluate preliminary indications of treatment effects, and to inform a power calculation for a potential randomized controlled trial.

Results from the three objectives will inform whether and how a full randomized controlled study of neurofeedback with refugees can be carried out.

8. Methods
This is a pilot study, designed to evaluate the feasibility and indications of effectiveness of neurofeedback with trauma-affected refugees.

8.1 Number of participants (N): 40 participants.

8.2 Population:
Participants will be recruited among patients referred to treatment at the Competence Centre for Transcultural Psychiatry. The inclusion criteria are: being an adult (18 years or older) refugee or a person who has been family reunified with a refugee; having PTSD and psychological trauma experienced outside Denmark in the anamnesis. The exclusion criteria are current abuse of drugs or alcohol (F1x.24-F1x.26), severe psychotic disorder (defined as patients with an ICD-10 diagnosis F2x), or disorders involving mania (F30.1-F31.9).

8.3 Description of data and data collection
The study will include patients from November 2018 to June 2019.

The participants will be offered neurofeedback after the first or second phase of treatment at CTP. The first phase consists of 6 sessions with an MD with psychoeducation and, if needed, pharmacological treatment (following a predefined algorithm), while the second phase consists of 12-20 sessions with trauma-focused psychotherapy.

As the primary outcome measure, we will use the Harvard Trauma Questionnaire (HTQ)\textsuperscript{9}. As
secondary outcome measures, we will use the Hopkins Symptom Checklist-25 (HSCL-25)\textsuperscript{10}, the Sheehan Disability Scale (SDS)\textsuperscript{11}, the WHO-Five Well-being Index (WHO-5)\textsuperscript{12}, and the Hamilton interview-based rating scales for depression (Ham-D)\textsuperscript{13} and anxiety (Ham-A)\textsuperscript{14}. Furthermore, at end of the intervention, all participants will be asked to complete a combined Satisfaction and Acceptability Questionnaire (SAQ). The scales will be administered at baseline and again after 12 sessions. The HTQ, HSCL-25, SDS and WHO-5 are routinely used in clinical evaluations at the CTP, both in the initial assessment and in the evaluation of symptom levels during and after treatment. This makes them potentially available for transfer to this study. The extent of such transfers, the reason for doing so, and the procedures involved, are fully explained in later sections of this protocol.

Electroencephalography (EEG) will be recorded at the beginning and end of each session. Each recording will have a duration of three minutes. A cap with 21 electrodes is used for recording from 19 channels.

In-depth descriptions of the experience with neurofeedback will be collected in qualitative interviews with 5-6 patients. This will cover patients’ potential concerns about the intervention, particularly leading up to the first session, potential difficulties in understanding the procedure before eventually trying it, what attracted them to try the intervention, as well as whether—and if so how—it impacted their perceived stress and quality of life.

8.4 Application/acceptance from the Danish Data Protection Agency, the National Committee on Health Research Ethics: Approved

8.5 Analysis
The recruitment rate will be calculated based on the number of patients recruited and the number of patients who declined participation. The rate of people who decline before vs. after receiving full information about the study is also calculated. For the acceptability analysis, SAQ summary scores for each item will be published, along with a full report of comments about discomfort or potential adverse effects. For the symptom rating scales, the size and standard deviation of the outcome of each scale will be calculated. The mean difference and the effect size will be described with 95%, 85% and 75% confidence intervals. If the 75% confidence interval includes the mean difference value of zero, this indicates substantial uncertainty about whether any symptom change has occurred\textsuperscript{15,16}. Similarly, if the 95% confidence interval of Cohen’s d does not include or exceed .3, this provides poor evidence that a minimum important symptom change has occurred\textsuperscript{16,17}. EEG data will be analyzed in WinEEG to describe changes both within sessions (before and after each neurofeedback intervention) and over the treatment course.

9. Expected results
This pilot study evaluates a relatively new treatment for a severely distressed population. If results are positive, they will inform a full-scale randomized controlled trial at the CTP, investigating the optimum role of neurofeedback across subgroups of patients and among established treatment options, such as psychopharmaceuticals and psychotherapy.

10. Dissemination of results
Results will be published, regardless of findings, in an international peer-reviewed journal.

11. References
1. Carlsson J, Sonne C, Vindbjerg E, Mortensen EL. Stress Management versus Cognitive Restructuring in


