CEBA Chronic Fatigue following acute Epstein-Barr Virus Infection in Adolescents

AKERSHUS UNIVERSITETSSYKEHUS

# Statistical analysis plan – CEBA part 2

## 1. AIM, STUDY DESIGN, VARIABLES

### Design overview

In total, the CEBA project encompasses a prospective, a cross-sectional, and a randomised controlled intervention (RCT) design (Figure 1). For the prospective and cross-sectional part (CEBA part 1), a total of 200 adolescents with acute EBV infection will be included and followed for 6 months, as well as 70 healthy subjects for cross-sectional comparisons. A separate statistical analysis plan has been developed for this part of the project (1).

The proportion of included EBV-patients that has a sum score of dichotomized responses ≥ 4 on the Chalder Fatigue questionnaire (4) at 6 months, is defined as chronic fatigue syndrome (CFS/ME) cases (7) and will be eligible for the RCT part (CEBA part 2, ClinicalTrials ID NCT02499302), which is outlined in detail in a separate study protocol (3) and described more shortly in the present document. The patients included in CEBA part 2 are reexamined at 9 months and 21 months; ie. 12 weeks and 52 weeks after the RCT baseline.

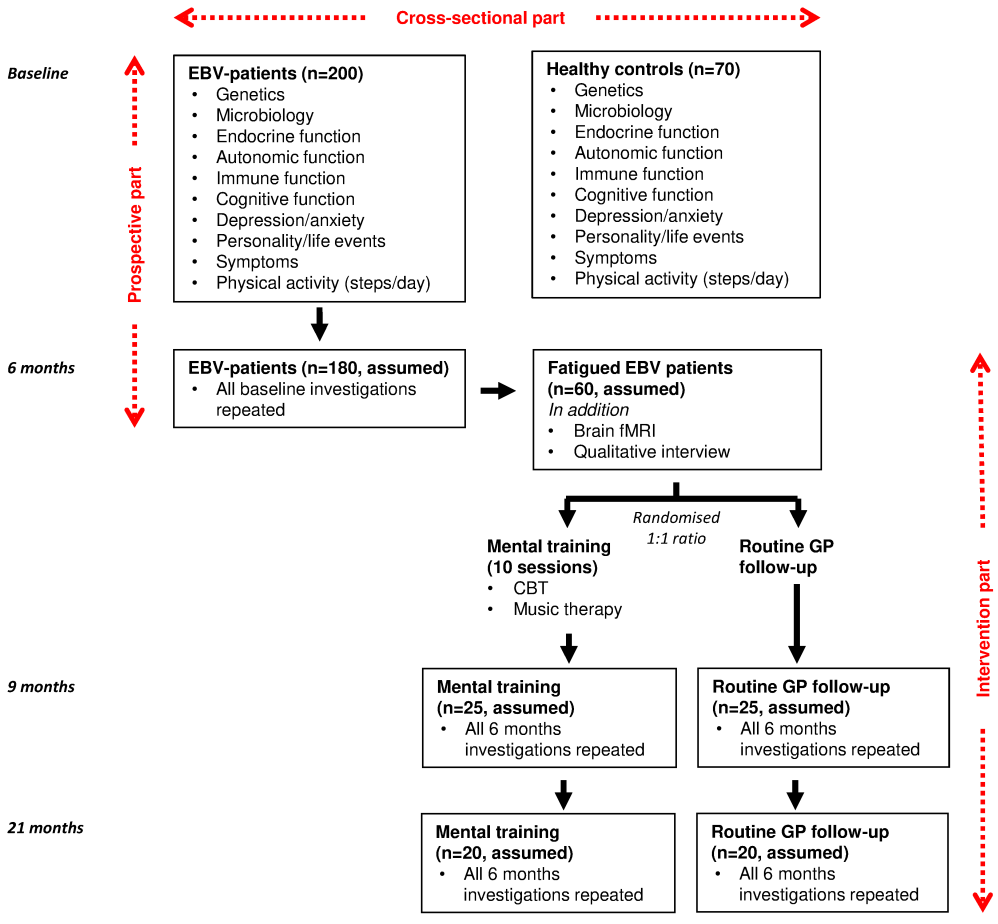


*Figure 1. Design overview of CEBA. This document concerns CEBA part 2, ie. the right lower part of the figure.*

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## Aims

The present study explores an individually tailored mental training program built upon cognitive behavioral therapy (CBT) and music therapy to adolescents suffering from CFS/ME after EBV-infection. The general aims are:

a. To investigate the clinical effects of the training program, in particular the effect on physical activity (primary endpoint) and symptoms (fatigue, pain, insomnia).
b. To investigate the effect of the training program on important elements in CFS/ME pathophysiology, such as cardiovascular autonomic control, the HPA-axis, inflammation, cognition, affect consciousness and functional brain networks.

Patients will be recruited according to the criteria specified in Table 1.

**Table 1. Criteria for inclusion and exclusion in the CEBA study**

| *Inclusion criteria* | *Exclusion criteria* |
|---|---|
| **Criteria for the prospective and cross-sectional part (*applies to both patients and healthy controls)** | |
| Age ≥ 12 years and < 20 years* | Debut of illness > 6 weeks ago (anamnestic) |
| Serological confirmation of acute EBV infection | Pregnancy* |
| Lives in one of the following Norwegian counties: Oslo, Akershus, Buskerud, Vestfold, Østfold* | Medical treatment for another disease (hormonal conterception and antibiotics against tonsillitis/pharyngitis are accepted)* |
| **Additional criteria for the intervention part (the present protocol)** | |
| CFS at 6 months (a sum score of dichotomized responses ≥ 4 on the Chalder Fatigue questionnaire) | Other illnesses that might explain the fatigue<br>Bedridden |

## Intervention – the mental training program

The intervention consists of one introductory session followed by 9 individual therapy sessions (one each week) of 1.5 hours duration and related home-work, combining elements from CBT and music therapy (Figure 2). Important elements of the mental training program are:

- Psychoeducation: Theories of CFS/ME pathophysiology and treatment rationale
- Relaxation: Bodily stress reduction, mindfulness
- Visualization: Contact with positive emotions, techniques of worrying reduction
- Experiences: Behavioral 'experiments' (individually adjusted)
- Cognitive challenges: Challenging thoughts about disease process, stimulus and outcome expectancies, prognosis

A detailed treatment manual has been developed (2).

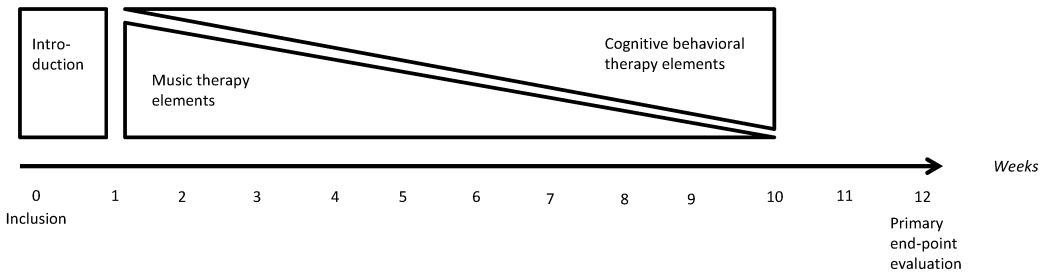


*Figure 2. Principles of the mental intervention program*

## Randomizing and blinding

Patients eligible for the present study are randomized to either mental training or routine follow-up by the general practitioner (GP) in a 1:1 probability by a computer-based routine for block randomization; block size will vary randomly between 4 and 6. Allocation concealment will be ensured using sequentially numbered, opaque, sealed envelopes. It is not possible to blind for treatment. However, during endpoint-

evaluation, the responsible researchers will be blinded for group allocation. Likewise, both patients and therapist will be blinded for the result of the end-point evaluation.

**Investigational program**

At baseline, all participants are subjected to a standardized investigational program. They will be instructed to fast overnight and abstain from tobacco products and caffeine at least 48 hours. The following elements are included:

- Clinical examination
- Pain threshold assessment
- Assessment of autonomic cardiovascular control
- Cognitive assessment
- Sampling of biological material (blood, hair, urine)
- Questionnaire
- Brain fMRI
- Qualitative interview

Following the in-hospital assessment, daily physical activity will be monitored during seven consecutive days using the *activPAL* accelerometer device (PAL Technologies Ltd, Scotland) (5)

**Effect monitoring**

The patients are thoroughly assessed at week 12 and week 52 by an investigational program identical to the one performed at inclusion. The primary end-point is physical activity at week 12, operationalized as mean steps/day count during seven consecutive days. Secondary end-points are:

- Biomarkers (week 12 and week 52).
    - Plasma catecholamines
    - Urine cortisol/creatinine ratio
    - Cytokine network
    - Number of NK-cells
    - Plasma gene expression profiles
- Autonomic cardiovascular control (week 12 and week 52).
    - Supine heart rate (HR) and heart rate variability (HRV)
    - HRV during fixed breathing rate
    - HR and blood pressure responses to upright posture
- Cognitions/neurobiology (week 12 and week 52).
    - Working memory (digit span test)
    - Cognitive inhibition (color-word interference test, condition 3)
    - Salience network connectivity (brain fMRI)
- Symptoms/function (week 12 and week 52).
    - Fatigue score (Chalder fatigue questionnaire)
    - Pain scores (Brief pain inventory)
    - Quality of life-score (Peds QL)
    - Anxiety and depression scores (HADS)
    - Alexithymia score (TAS-20)
    - Insomnia score (KSQ)
    - Pain threshold
    - Disability score (FDI)
- Qualitative interview responses (week 12 and week 52).
- Physical activity (mean step/day) at week 52.

**Side effects and unexpected events**

A separate questionnaire addressing possible side effects, unexpected events, complications etc. related to the mental intervention is developed. This questionnaire will also chart other variables of interest, such as other therapies for chronic fatigue instituted by the GP. The participants will complete this questionnaire three times during the intervention period (week 3, week 6 and week 9), and also during the end-point

evaluation at week 12. The answers to the questionnaire will be analyzed and published together with the rest of the trial results

## 2. POWER CALCULATION

Based upon experiences from the NorCAPITAL project we assume a drop-out rate of 10 % in the prospective part of the CEBA project (8), leaving a total of 180 patients to evaluation at 6 months. Previous studies indicate that up to 1/3 might suffer from chronic fatigue (6); thus, 60 patients might be eligible for the present study. Assuming that 5 % will decline participation, and another 10 % drop-out rate during the intervention period, 50 participants will be available for endpoint evaluation (8).

The primary end-point in the present study is mean steps/day during seven consecutive days 12 weeks after inclusion. In the NorCAPITAL project, the mean (standard deviation) steps/day count for CFS/ME adolescents was approximately 4500 (2400) (8). In the present study, the power to detect an increment of 2000 steps/day is at least 80 % ($\alpha$=0.05). This effect size is rather large (0.8 times the standard deviation); however, as CBT alone is documented to have moderate effect size in CFS/ME, only a substantial effect size is of direct clinical interest. Analogously, only a substantial treatment effect is of interest regarding markers of pathophysiology.

## 3. ANALYSIS SETS

**Full analysis set**
The 'full analysis set' is defined as all patients who were randomized to mental training/routine follow-up (Figure 2). This 'full analysis set' will be used for intention-to-treat analyses of efficacy. Missing values will be imputed based on the principle of 'last observation carried forward' (LOCF). In composite variables, "LOCF mixed components" will be used; that is, if only part of a composite variable is missing, that specific part will be imputed from the last observation

**Per protocol analysis set**
The 'per protocol analysis set' is defined as all patients in the 'full analysis set' that completed the treatment period (12 weeks) without any of the following protocol deviations:

- Interruption of therapy.
- Lost to follow-up.
- Primary endpoint measurements missing.
- Diagnosed with another chronic disorder during the study period.
- Experiencing a severe illness or trauma during the study period.
- Commencing other treatment for CFS/ME during the study period.

Missing data will not be imputed in the per protocol analysis set.

## 4. STATISTICAL METHODS

**General considerations**
Continuous variables will be reported with parametric (mean/standard deviation) or non-parametric (median, quartiles) descriptive statistics, depending on the distribution. Ordinal/nominal variables will be reported as frequency tabulation. All statistical tests will be carried out two-sided. A p-value $\leq 0.05$ is considered statistically significant. For statistical tests of intervention outcome (cf below), variables having a skewed distribution will be transformed in order to achieve a normal distribution.

**Analyses of intervention effect**
Intention-to-treat analyses (full analysis set) will be used to compare the group allocated to mental training with the group allocated to routine follow-up using general linear models (ANCOVA). The baseline values

of each efficacy endpoint will be included as covariates. The null hypothesis is no differences in efficacy variables between the two treatment allocation groups. Primary endpoint is mean step/day count during 7 consecutive days at week 12. For each statistical analysis, the net intervention effect (the mean change in the mental intervention group minus the mean change in the routine follow-up group) will be estimated from the parameters of the fitted general linear model and reported with 95 % confidence interval. An identical methodological approach will be applied for per protocol analyses based upon the per protocol analysis set.

Safety data will be summarized descriptively through appropriate data tabulations and descriptive statistics. No interim analysis will be carried out.

## 5. REFRENCES

All CEBA documents (protocol, treatment manual, statistical analysis plan etc.) is available at http://www.ahus.no/omoss_/avdelinger_/barne-og-ungdomsklinikken_/forskning_og_utvikling_/Sider/CEBA.aspx

1. CEBA part 1 – Statistical analysis plan. Lørenskog: Dept. of Pediatrics, Akershus University Hospital, 2015.
2. CEBA part 2 - Manual for the mental training program. Lørenskog: Dept. of Pediatrics, Akershus University Hospital, 2015.
3. CEBA part 2 - Protocol. Lørenskog: Dept. of Pediatrics, Akershus University Hospital, 2015.
4. Chalder T, et al. Development of a fatigue scale. J Psychosom Res 1993 ; 37 : 147-53.
5. Dahlgren G, et al. Test-retest reliability of step counts with the ActivPAL device in common daily activities. Gait Posture 2010; 32: 386-90.
6. Katz BZ, et al. Autonomic symptoms at baseline and following infectious mononucleosis in a prospective cohort of adolescents. Arch Pediatr Adolesc Med 2011; 165: 765-6.
7. Loge JH, et al. Fatigue in the general Norwegian population: normative data and associations. J Psychosom Res 1998; 45: 53-65.
8. Sulheim D, et al. Disease mechanisms and clonidine treatment in adolescent chronic fatigue syndrome: a combined cross-sectional and randomized clinical trial. JAMA Pediatr 2014; 168: 351-60.