Mental training for chronic fatigue syndrome (CFS/ME) following EBV infection in adolescents: a randomised controlled trial

1. Introduction

Context
Chronic fatigue syndrome (CFS) or myalgic encephalomyelitis (ME) is characterized by unexplained, disabling and long lasting fatigue, as well as pain, impaired memory, sleep difficulties and other symptoms (RCPCH 2004; IOM 2015). In Norway there are about 600 patients under the age of 18 that suffer from CFS/ME (Nijhof 2011). The disability is substantial, and many patients are absent from school, loose contact with friends and are physically inactive. Family functioning might be severely affected (Missen 2012). Treatment options are sparse. Due to the high prevalence, severe disability and limited treatment options, this illness has profound economic impact on society. The Norwegian Labour and Welfare Administration (NAV) estimates the insurance expenses to NOK 500 mill/year. In the US, the total annual cost was estimated to be $9 billion in 2004 (Reynolds 2004).

Epstein-Barr virus (EBV) is a member of the herpes virus family. In adolescents and in young adults, acute EBV infection often causes infectious mononucleosis characterized by high fever, sore throat and swollen lymphatic glands. A significant proportion of patient develops long-lasting fatigue following the acute illness, and EBV-infection is considered an important precipitating cause of CFS/ME. Accordingly, previous studies indicate that about 20 % of all adolescents with infectious mononucleosis fulfil narrow diagnostic criteria for CFS after 6 months, whereas approximately 10 % fulfil these criteria after one year (Katz 2011; Hickie 2009).

Thus, a study of acute EBV infection might provide a “window” on CFS disease mechanism. The CEBA project (Chronic fatigue following acute Epstein-Barr virus infection in Adolescents; ClinicalTrials ID: NCT02335437) is a combined prospective and cross-sectional study of 200 adolescents suffering from acute EBV infections and 70 healthy controls of similar age- and gender distribution (Figure 2). The primary aims are to identify factors that predispose to CFS/ME 6 months after the acute infection, and to compare pathophysiological features of patients with a group of healthy controls. Thus, this project will provide a sample of thoroughly characterized CFS/ME patients, all having the same precipitation factor (EBV-infection). Subject inclusion in CEBA commenced March 1st 2015; data collection is assumed to be completed by September 2016.

The present project is an intervention trial in the subgroup of CEBA patients that has developed CFS/ME 6 months after the acute EBV infection.

Aim
The general aim of this study is to investigate the effect of an individually tailored mental training program in adolescents developing CFS/ME after an acute EBV infection. Endpoints include physical activity (primary endpoint), symptoms (fatigue, pain, insomnia), cognitive function (executive functions) and markers of disease mechanisms (autonomic, endocrine, and immune responses).

Strategic considerations
• Patient group. In Dec. 2012, the Norwegian Minister of Health publicly stated (my translation) (http://www.facebook.com/jonasgahrstore/posts/10151319853934238): “… research related to causes and treatment of CFS shall be prioritized …” Likewise, stronger research efforts on CFS/ME have been demanded from international organisations (IOM 2015), the Norwegian Parliament (Solberg 2011), a recent HTA report (SINTEF 2011),
and patients’ organizations. Accordingly, such research is given high priority in the Governing Document from Department of Health to Health South-East.

- **Gender issues.** CFS/ME is far more common among females than males, the ratio being about 3:1, as has been documented in a recent Norwegian study (Bakken 2014). Thus, CFS is a typical ‘women’s disease’, with strong impact on women’s health, but traditionally receiving low attention scientifically and clinically. In this project, possible gender differences will receive strong attention in the data analyses.

- **Relevance and benefit to society.** This project addresses a highly challenging health problem nationally and internationally: Prevalence is high, disability is severe, treatment options are limited, and there is a strong negative impact upon employment issues, social security systems, family networks etc. The Norwegian Labour and Welfare Administration (NAV) estimates the insurance expenses to NOK 500 mill/year. In the US, the total annual cost for the society has been estimated to $9 billion (Reynolds 2004).

- **Previous research experiences.** This study is integrated in the CEBA project on adolescent CFS/ME, and will use data recorded in this projects (ref. CEBA protocol). The study is also strongly related to the NorCAPITAL project (ref. NorCAPITAL protocol), which was a combined cross-sectional and randomised controlled trial on adolescent CFS/ME with which 5 PhD students were affiliated. Thus, external validity as well as feasibility is ensured.

- **Research organization and collaboration.** NorCAPITAL data acquisition was finished in November 2012. A total of nine papers from this project have been published in international medical journals; three additional papers are under review. The CEBA project commenced patient inclusion 2015/3/1; data acquisition is assumed to be completed by October 2016. Overall the PAEDIA research group that conducts these projects has been responsible for 27 scientific papers, 6 congress abstracts and 5 popular papers in the field, making it the most productive CFS/ME research group in Norway. The group has established national and international collaboration with highly reputed research groups. Also, there are strong relations to political and administrative bodies as well as mass media, securing wide dissemination and practical impact of the results.

- **Research profile and impact.** This study has a clinical scope, but includes multidisciplinary and translational perspectives, as it encompasses endocrine, autonomic and immunological perspectives. Furthermore, the project has direct clinical relevance and also lays the foundation for further research.

- **Institutional strategy and support.** High-quality research at the interface of patient care is an overriding vision for Akershus University Hospital. This study also complies with the scientific and clinical competence on a) CFS/ME, b) adolescent medicine and c) pediatric infections at the Dept. of Pediatrics, AHUS University Hospital.

## 2. Background

**EBV-infection as a trigger of CFS/ME**

The precise role of microorganisms in CFS remains unsettled (Bansal 2012). However, it is generally accepted that certain infections, such as acute EBV infection, might precipitate the condition (Hickie 2009), and previous studies indicate that up to 1/3 of all adolescents with EBV-infection might suffer from chronic fatigue after one year (defined as a sum score of dichotomized responses ≥ 4 on the Chalder Fatigue questionnaire) (Katz 2011). Accordingly, EBV-infection is often characterized by long-lasting fatigue, also in adolescents that do not develop CFS, and there appears to be similarities regarding autonomic alterations (Katz 2011). Still, EBV infection alone does not appear to be a sufficient cause; it should rather be
regarded an ingredient of a multifactorial causation mechanisms in concert with other predisposing, precipitating and perpetuating factors (IOM 2015).

Other background factors in CFS/ME – personality traits and critical life events
Studies indicate that personality traits, such as high levels of conscientiousness, might predispose to CFS (White 2000; van Geelen 2007). Furthermore, critical life events might precipitate the disorder (Theorell 1999).

Critical life events, as well as infections, normally elicit a similar neurobiological stress response – or ‘arousal’ - characterized by activation of autonomic, endocrine and immune compensatory mechanisms (Goldstein 2001). A long-lasting biological or psychological challenge causes a comparably prolonged arousal response, and in certain cases, the arousal response might be insufficient in solving the initial problem (Ursin 2004). An attempt of compensation would be to generate a stronger one. As there is no apparent solution to the individual, such attempts might be perceived as inadequate, resulting in negative stimulus and response outcome expectancy. Thus, a vicious circle is established, as the evaluation of the arousal response depends upon expectancies: negative expectations reinforce the arousal response (Ursin 2004). This inappropriate learning process can be strengthened by attentiveness, corresponding with reports of increased focus on bodily sensations in CFS (Heijmans 1998). Increased worry about coping abilities is also suggested to be a risk factor (Brosschot 2006), complying with personality traits that might be associated with CFS (Kato 2006).

Pathophysiology of CFS/ME
The pathophysiology of CFS remains poorly understood. Previous adolescent studies report enhanced sympathetic and attenuated parasympathetic cardiovascular nervous activity, causing increased levels of plasma catecholamines, increased resting heart rate and enhanced cardiovascular responses to upright posture (Wyller et al 2011; Wyller AJC 2007; Sulheim 2014). Also, attenuation of the hypothalamus-pituitary-adrenal axis (HPA-axis) seems to be a central feature (Papadopoulos 2012; Sulheim 2014). Recent evidence suggests a relationship between perceived stress-management skills, the symptom of post-exertional malaise (which by many researchers is considered a hallmark of CFS/ME), and the cortisol awakening response (Hall et al 2014). Furthermore, low-grade systemic inflammation (Klimas 2012) has also been reported, but a recent study did not find any difference in cytokine networks (Wyller 2014). Finally, neuropsychological studies suggest impairments of executive control functions such as working memory and cognitive inhibition (Sulheim 2015).

‘Sustained arousal’ – a model for disease mechanisms in CFS
One proposed model of how these different features might interact is the ‘sustained arousal’-model, suggesting that a persistent neurobiological stress response constitutes a vital part of the underlying disease mechanisms in CFS/ME (Figure 1) (Wyller BBF 2009). The model integrates empirical findings from different areas, such as altered autonomic cardiovascular control (Sulheim et al 2014; Wyller et al 2011; Wyller AJC 2007), low-grade systemic inflammation (Klimas 2012), attenuation of the HPA-axis (Papadopoulos 2012) and impairment of executive control functions (Sulheim 2015). Importantly, it directly suggests that CFS/ME is associated with functional central nervous system alterations, as has recently been documented by our group (Wortinger 2015).

The ‘sustained arousal’-model suggests an explanation for the well-documented beneficial effect of cognitive behavioral therapy (CBT) and graded exercise therapy (GET) (Nijhof 2012; White 2011; Larun 2015). Furthermore, the model complies with other recent CFS models (Maloney 2012; Nijs 2012) and rests upon contemporary stress theories.
(Goldstein 2001; McEwen 1998; Ursin 2004). However, alternative models exist; in particular, the conceptualization of CFS/ME as an autoimmune disorder, possibly trigged by an infection, has been strongly advocated by many researchers (Carruthers 2011; Fluge 2011).

**Figure 1. The sustained arousal-model of CFS (adopted from (Wyller 2009) and simplified).**

**Affect consciousness in CFS/ME**

To achieve better outcomes and facilitate recovery in CFS/ME, other mechanisms have been identified that may play a role in both development and maintenance of the disorder. One such mechanism is **reduced affect consciousness**, referring to the ability to adequately perceive, tolerate, reflect upon and express (verbally and nonverbally) discrete emotions (Solbakken, Hansen, Havik 2011). Furthermore it reflects the ability to both access and use emotions as signals, utilizing the adaptive properties of affects for personal adjustment (Solbakken, Hansen, Monsen 2011).

Several lines of research support the investigation of affect consciousness in CFS patients: First, those with particularly low affect consciousness have a tendency to focus on somatic sensations that accompany emotional activation and to misinterpret these as signs of illness (Taylor 2004). Individuals with low affect consciousness are therefore considered vulnerable to incorrectly attribute innocent bodily sensations to physical disease, for which subsequently no medical explanation can be found (Kooiman 2004). This is in line with a number of studies reporting that CFS patients have a tendency to interpret bodily sensations as sign of physical disease (Dendy 2001). For example 86% of patients with fatigue syndrome attributed their fatigue to physical factors in one study (Wessely 1989). CFS patients are also shown to be more prone to attribute bodily sensations to illness and less likely to interpret these symptoms in terms of **negative emotion**, compared to both healthy adults and patients with multiple sclerosis (MS) (Dendy 2001).

Second, the CATS theory is based on the James-Lange theory of emotion. This theory states that any event leading to a change in bodily arousal is subject to interpretation, which causes a subjective feeling or response (Ursin 2010). This theory reflects how William James separated the concept of emotions (crude bodily signals) from feelings (learned cognitions). According to the two-step theory of anxiety, this would mean that when patients interpret...
feelings as symptoms of illness or fatigue, they would be prone to fear and avoid these feelings. This again leads to a process where they attempt to cognitively avoid the feared stimuli, often using worry as a problem-solving strategy (Wells 2011).

Third, such cognitive avoidance is the hallmark of the perseverative cognition hypothesis, a cognitive analogue to the CATS theory (Brosschot 2006). This hypothesis states that patients with complex and unspecific health complaints tend to worry over their situation, directing their attention to stressors and the lack of coping, sustaining a central, cognitive activation. This could lead to a sensitization of normal and necessary signals from the body. The signals may acquire an increased value and attention, to such an extent that normal somatic feedback becomes overwhelming somatic complaints and is experienced as musculoskeletal pain and/or fatigue (Brosschot 2006). Hence, investigating low affect consciousness in patients with CFS/ME may evolve our understanding of mechanisms behind the sustained activation model, which is regarded as the most comprehensive and empirical understanding of long-term fatigue syndromes (Wyller BBF 2009).

A related concept to affect consciousness is alexithymia, a personality construct characterized by difficulties identifying and describing one’s own feelings. Alexithymia is understood as particularly low affect consciousness. In contrast to affect consciousness that is considered a function, alexithymia is regarded as a personality trait. Alexithymia is considered an important risk factor for the development of medically unexplained physical symptoms, a definition including CFS/ME (van der Putte 2007).

There is some preliminary evidence for alexithymia/reduced affect consciousness in CFS patients. Van de Putte et al. examined the prevalence of alexithymia among 40 adolescent outpatients diagnosed with CFS/ME and 36 healthy controls. A proportion of 30% (12 patients) fulfilled criteria for alexithymia compared to one (1) healthy adolescent. The CFS/ME adolescents reported lower function on the subscales tasked with identifying feelings and expressing feelings. Adjusting for depression and anxiety, only the subscale identifying feelings remained statistically significant (van der Putte 2007).

To the best of our knowledge this is the only study on affect consciousness in adolescence with CFS/ME. However, adult CFS patients are reported to have more negative beliefs about experiencing and expressing negative feelings than healthy individuals (Rimes 2010). Moreover, adults with CFS report to a greater extent than healthy adults a belief that expressing negative emotions to others is unacceptable and a sign of weakness (Rimes 2010), but this has not been investigated in young patients. This may prevent CFS patients from experiencing situations where they could receive help to label and understand their emotions (referring to components of affect consciousness), a prerequisite for regulation of emotions (Fonagy 2004).

While some preliminary evidence for reduced affect consciousness in CFS patients exists, little is known about the role of affect consciousness in the development and maintenance of the disorder. Moreover, studies concerning alexithymia in adolescents with CFS are non-existent.

Cognitive behavioral therapy in CFS/ME
Despite strong research efforts, no pharmaceutical has been proven beneficial in CFS/ME. In contrast, evidence suggests a beneficial effect of mental techniques, and CBT in particular (Smith 2013). For instance, in the PACE trial of 641 adult CFS/ME patients, CBT had a beneficial effect on fatigue scores as compared to specialist medical care or adaptive pacing therapy (White 2011). The effect size was moderate, however, with a mean fatigue score difference (Chalder fatigue questionnaire, range 0-33 (Chalder 1993)) of 3.4 from baseline to the end of the intervention period. There were no differences in the frequencies of adverse effects across treatment groups, thus CBT was considered perfectly safe in the population.
under study (Dougall et al. 2014). Effect size might be larger in adolescents; in the FITNET study of 148 adolescent CFS/ME patients (in which the CBT was given by email-consultations), the mean fatigue score (CIS-20, range 8-56) difference across the two intervention groups was 18.3 (Nijhof 2012). This effect remained stable at long-term follow-up (Nijhof 2013). In another study of 71 adolescent patients, the patients allocated to CBT (10 individual sessions, traditional techniques) as opposed to waiting list had a mean fatigue score difference of 14.5 (CIS-20, range 8-56) (Stulemijre 2005). A third study of 159 adolescents combined CBT and biofeedback (to develop relaxation and coping strategies in relation to symptoms), and reported a mean fatigue score difference of 12.2 (CIS-20, range 8-56) in favor of the intervention (Al-Haggar et al 2006).

Little is known on the mechanisms by which CBT improves chronic fatigue; however, a recent report suggests that patients’ sense of control over fatigue, their perceived activity and their self-reported physical functioning is of importance, whereas objective physical activity is not a process variable (Heins 2013). Similarly, a study on pragmatic rehabilitation of CFS/ME (which included elements from CBT and GET) suggested that patients’ belief about fatigue and activity (in particular their beliefs about the importance of activity limitation) is important for the effect of the intervention, whereas activity level per se is not a mediator of treatment effect (Wearden 2013). Recent evidence also suggest that therapy should be individually tailored according to co-morbid depression and anxiety, as certain perpetuating factors might differ: Beliefs about damage and symptom focusing were more frequent in patients with anxiety disorders while embarrassment and behavioral avoidance were more common in patients with depressive disorder (Cella 2013). In contrast, a history of childhood maltreatment should not necessarily lead to individual adjustment of a fatigue therapy program (Heins 2011).

The studies on CBT in CFS/ME have been criticized from different angels. First, the exclusion of the most severely disabled patients and a relatively short disease duration period prior to inclusion questions the general generalizability (Shinohara M 2011). Second, the trials were not standardized in terms of precipitating event; it might be, for instance, that the overall effect in favor of CBT was due to a subgroup whose main causes of CFS/ME were “pure” mental stressors, whereas patients suffering chiefly from infectious or autoimmune mechanism might not have any effect of CBT at all. Third, no potential biomarkers were recorded in relation to the clinical outcome variables, thus it is not possible to relate an eventual improvement of symptoms or function to possible underlying pathophysiological mechanisms (Fisher et al 2014).

Other mental techniques in CFS/ME
In addition to CBT, related mental techniques have been studied. Mindfulness-meditation is related to improvement of symptoms and function in CFS/ME (Lakhan 2013). The Lightning Process (LP) is a trademarked intervention with elements from CBT as well as other psychological therapies (such as neuro-linguistic programming), delivered over three consecutive days as group sessions. LP has gained popularity among Norwegian CFS/ME sufferers, but has also received strong criticism; so far, there are no reported studies on the effectiveness (Crawley 2013).

It has been argued that a multidisciplinary approach, combining CBT with other intervention elements, might improve treatment effectiveness (Van Houdenhove 2008; Price 2008). While theoretically attractive, such approaches have been scarcely studied, and there exist only a few, uncontrolled reports: In adolescents, Viner and co-workers reported strong treatment effects of a multidisciplinary rehabilitation program featuring CBT, GET, family sessions and supportive care (Viner 2004). A randomized controlled trial of multidisciplinary
rehabilitation in adults CFS/ME patients is under way (Vos-Vromans 2012), but to the best of our knowledge, no such trial has been planned or undertaken in adolescents.

**Music therapy as a possible adjunct in a CFS/ME treatment program**

Music therapy is an evidence-based complementary therapy form used in many different clinical contexts (Bonde, 2014). A number of Cochrane reviews report that music therapy has positive effects in cancer (Bradt, Dileo, Grocke, & Magill, 2011) schizophrenia (Mössler, Chen, Heldal, & Gold, 2011), heart diseases (Bradt & Dileo, 2009; Bradt, Dileo, & Potvin, 2013), mechanical ventilation (Bradt & Dileo, 2014), surgery (Bradt, Dileo, & Shim, 2013), end-of-life care (Bradt & Dileo, 2014b), pain (Cepeda, Carr, Lau, & Alvarez, 2006), acquired brain injury (Bradt, Magee, Dileo, Wheller, & McGilliway, 2010), and autism spectrum disorders (Geretsegger, Elefant, Mössler, & Gold, 2014). Music therapy can be expressive, e.g. using songwriting or improvisation, or receptive, using music listening, relaxation and imagery to achieve therapeutic goals. Embodiment, emotional and relational experiences in a non-verbal medium, and regulation of arousal are core elements in clinical music therapy.

There are no existing studies of music therapy with CFS/ME clients. However, music therapy has been used with good effects in patients with related problems e.g. fibromyalgia, where the combination of music, therapeutic relationship and group bonding enhance the potential to feel, think about and verbalize certain underlying emotions, feelings and beliefs (Bjellånes, 1994; Torres, 2015). Listening (to music) and feeling listened to (by the therapist) allowed patients to open up to a recognition and expression of their life experiences. Accepting and sharing these experiences, making sense of what is happening to them and why, paves the way for other ways of relating to life itself. Another example is music therapy with long-term sick leave due to stress, where music listening (i.e. Guided Imagery and Music) decreased bodily stress symptoms, increased energy and well-being, enhanced coping with inner and outer conflicts, helped to overcome traumatic work experiences, provided new relational competencies, improved mood and gave access to hope for the future work life (Beck, 2012, 2015).

A Swedish twin study with 8000 participants (Theorell et al., 2014) tested the hypothesis that musical activities may contribute to the prevention of alexithymia. The study documented that “musical achievement and musical practice are associated with lower levels of alexithymia in both men and women. Musical engagement thus appears to be associated with higher emotional competence, although effect sizes are small”. Thomas Wosch (Wosch et al., 2005) reported that music therapy can reduce alexithymia in different client groups, e.g. patients suffering from depression (Erkkilä et al., 2011). Accordingly, Trondalen has argued that people suffering from an eating disorder promote on music therapy e.g. through a self-listening procedure. The patient and the music therapist, with a similar, however, not identical music experience, listens to a recording of their own improvisation, performance, or composition, and reflect upon themselves and the experience. This procedure supports identification of inner feelings states and a verbal description of these, as well as supporting imaginal capacities (Trondalen, 2004).

Human beings construct reality by mental representation of the world. It is not the world itself, but representations that can be shared, while understanding oneself and others as active contributors and co-creative individuals; that is “mentalization” (Fonagy, Gergely, Jurist, & Target, 2002). Music is an immediate and non-verbal experience. Through a joint musical experience, be it through songwriting, improvisation or music listening, non-verbal experiences can be explored and shared in an intersubjective setting. Such a sharing and joint attention based on a joint experience contribute to a merger of cognitive, emotional and reflective perspectives into one unit, while grasping and representing such a double reality through an endeavor to explore and recognize the relationship. Such a development means an
abstraction from immediate and concrete experience. New feelings and symbolic meaning emerge, and these novelties can especially be explored through music, as a multi-layered phenomenon (Frohne-Hagemann, 2015; Trondalen, 2015 to be published).

There is a long tradition of music therapy based on cognitive principles in the USA (Bonde, Trondalen & Wigram, 2014; Standley et al, 2004). However, in Scandinavia music therapy has been based more on either psychodynamic, humanistic-existential or community principles (Bonde, 2014; Trondalen & Ruud, 2008). Combinations of music therapy and CBT, or integrating elements of CBT in music therapy, have recently been tried out in different clinical contexts, especially in psychiatry (Lund, 2012; Moe, 2007). Important elements in such integrated approaches are: a) the implementation of cognitive techniques and methods in the sessions, e.g. ideas from Acceptance & Commitment Therapy, “examining the value system”, the “cognitive diamond”, working with lists of positive and negative events and thoughts, formulation of specific goals and activities; b) the inclusion of homework (the patient works min 15 min/day on music-related tasks, such as writing lyric notes, identifying helpful music, doing music/relaxation exercises).

Music therapy together with mindfulness supports an individual process allowing the music to take the patient where she needs to go in the moment. Mindfulness – like music — is experiential, allowing the patient to being aware in a non-attached and non-judgmentally way of things that happens in the moment (Kabat-Zinn, 2003). In music listening the exploration of feelings, memories, thoughts and perspectives that arise in response to the music can be accepted, understood and integrated into a renewed self-understanding (Trondalen & Oveland, 2008; Van Dort, 2015).

Treatment and prognosis
Although six months disease duration is considered sufficient for a diagnosis of CFS/ME (IOM 2015; Fukuda 1994, Carruthers 2011), most adolescents experience a considerable longer time period from the début of CFS/ME symptoms until a definite diagnosis is made (Knight et al. 2013). This protracted period is related to severe functional disability, and may also have a negative impact on prognosis (Joyce 1997, Werker 2013). These facts favor initiation of treatment at an early stage; however, to the best of our knowledge, no prior study has addressed the importance of early intervention for CFS/ME.

3. Aims
This study explores the effect of an individually tailored, multidisciplinary mental training program (in which CBT and music therapy are the main elements) to adolescents suffering from CFS/ME after EBV-infection. The general aims are:

a. To explore the clinical effect of the training program, in particular the effect on physical activity (primary endpoint) and symptoms (fatigue, pain, insomnia).

b. To explore 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.

Taken together, the study will provide important knowledge on clinical handling (aim a.) as well as disease mechanism (aim b.). Furthermore, it addresses the criticism regarding heterogeneity of precipitating factors and lack of biomarkers in clinical trials, and it explores the importance of early intervention. Finally, the individually tailored, multidisciplinary approach in the treatment group, as well as the routine follow-up in the control group are close to clinical everyday settings, giving the study high external validity.
4. Execution

Design overview

In total, the CEBA project encompasses a prospective design, a randomised controlled intervention design (the present protocol), and a cross-sectional design (Figure 2). For the prospective part, a total of 200 adolescents with acute EBV infection will be included and followed for 6 months. A similar investigational program is to be conducted at baseline (0 months) and 6 months. Those who suffer from chronic fatigue at 6 months (defined as a sum score of dichotomized responses ≥ 4 on the Chalder Fatigue questionnaire (Chalder 1993)) are eligible for inclusion in the randomized controlled intervention. This subgroup of the initial cohort will undergo supplemental investigations prior to the intervention, as well as a full investigational program immediately after the intervention and finally after 1 year. Finally, 70 healthy controls having the same distribution of gender and age as the patients will be included for cross-sectional comparisons.

Figure 2. Design overview of the CEBA project. The present protocol concerns the lower right panels.

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 (Sulheim 2014), leaving a total of 180 patients to evaluation at 6
months. Previous studies indicate that up to 1/3 might suffer from chronic fatigue (Katz 2011); 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 (Sulheim 2014).

The primary end-point in the present study is patients’ functional capacity, operationalized as mean steps/day count during a seven day period after 12 weeks of mental intervention. Mean (standard deviation) steps/day count for chronically fatigued adolescents was approximately 4500 (2400) in the NorCAPITAL project (Sulheim 2014). In the present study, the power to detect an increment of 2000 steps/day is at least 80% (α=0.05). This effect size is rather large (0.8 times the standard deviation); however, as CBT alone is documented to have small to moderate effect size in CFS/ME, only a substantial effect size is of direct clinical interest. Also, the FITNET study suggests that larger treatment effects might be assumed in adolescent CFS/ME patients as compared to adults (Nijhof 2012).

The precise meaning of “recovery” is much debated in the CFS/ME literature (Matthees 2014). In this study, we define recovery as a dichotomized Chalder fatigue score < 4; fatigue score is a secondary endpoint in the present study.

**Recruitment, inclusion and exclusion**

Inclusion in the prospective part of the CEBA project is based on serological confirmation of acute EBV infection. The Microbiological Laboratory at AHUS University Hospital and Fürst laboratory provides microbiological analyses for almost all General Practitioners in the hospital’s population area. Patients with acute EBV infection in the relevant age group will be consecutively identified, and a final decision on inclusion will be taken during the initial phase of the first clinical encounter at baseline (see below). The proportion of included EBV-patients that suffer for chronic fatigue 6 months after inclusion (defined as a sum score of dichotomized responses ≥ 4 on the Chalder Fatigue questionnaire) will be eligible for the present study.

<table>
<thead>
<tr>
<th>Criteria for inclusion and exclusion</th>
<th>Exclusion criteria</th>
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<tr>
<td><strong>Inclusion criteria</strong></td>
<td><strong>Criteria for the prospective part of CEBA</strong></td>
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<tr>
<td>Age ≥ 12 years and &lt; 20 years</td>
<td>Debut of illness &gt; 6 weeks ago (anamnestic)</td>
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<td>Serological confirmation of acute EBV infection</td>
<td>Pregnancy</td>
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<td>Lives in one of the following Norwegian counties: Oslo, Akershus, Buskerud, Vestfold, Østfold</td>
<td>Medical treatment for another disease (hormonal contraception and antibiotics against tonsillitis/pharyngitis are accepted)</td>
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<tr>
<td>Chronic fatigue at 6 months (a sum score of dichotomized responses ≥ 4 on the Chalder Fatigue questionnaire)</td>
<td>Other illnesses that might explain the fatigue</td>
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<td>Bedridden</td>
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**Investigational program**

At 6 months follow-up in the prospective part of CEBA, all participants are subjected to a standardized investigational program. All participants will be instructed to fast overnight and abstain from tobacco products and caffeine at least 48 hours. The following elements are included in all participants (for details, see below):

- Clinical examination
- Pain threshold assessment
• Cardiovascular assessment
• Cognitive assessment
• Sampling of biological material (blood and urine)
• Questionnaire

In addition, patients suffering from chronic fatigue, and who is therefore eligible for inclusion in the randomised controlled part, will undergo
• 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).

**Clinical examination**

The clinical examination includes auscultation of the heart and lungs, palpation of the cervical lymphatic nodes, inspection of the throat and ears and palpation the abdomen. Percentile scores for weight/height and height/age will be recorded. In addition, the examination includes ultrasound measurement of splenic enlargement.

**Pain threshold assessment**

Pain threshold will be assessed by means of an algometer (Algometer Commander, JTECH Medical, Salt Lake City, USA). Anatomically well-defined “trigger-points” are subjected to increasing pressure; the patients alert at the point where the pressure is perceived to be painful (Harden 2007).

**Cardiovascular assessment**

At supine rest, participants will be attached to the Task Force Monitor® (Model 3040i, CNSystems Medizintechnic, Graz, Austria); a combined hardware and software device for noninvasive continuous recording of cardiovascular variables (Fortin 2006). A 5 minute baseline recording will be obtained. Thereafter, the participants are instructed to breathe at a fixed breathing rate of 0.2 Hz (12 breaths per minute) for 5 minutes. Finally, the participants are instructed to stand upright for 3 minutes.

Instantaneous heart rate (HR) is obtained from the R-R interval (RRI) of the electrocardiogram. Photoplethysmography on the right middle finger will be used to obtain a non-invasive, continuous recording of arterial blood pressure (Parati 1989). Impedance cardiography will be used to obtain a continuous recording of the temporal derivative of the transthoracic impedance (dZ/dt) (Denniston 1976). All recorded signals is on-line transferred to the built-in recording computer of the Task Force Monitor®, running software for real-time data acquisition.

**Cognitive assessment**

Participants will undergo cognitive testing in the following sequence: The digit span test from the Wechsler Intelligence Scale for Children, 4th edition (WISC-IV) (Wechsler 2003), the Color-Word Interference test from the Delis-Kaplan Executive Function System (D-KEFS) (Delis 2001), and the Hopkins Verbal Learning Test-Revised (HVLT-R) (Benedict 1998). In addition, two subtests form of the Wechsler Abbreviated Scale of Intelligence (WASI) will be used to estimate the patients IQ.

**Sampling of biological material**

Blood samples will be collected between 08.15 and 09.15 am. An ointment containing the local anaesthetic lidocaine (Emla®) will be applied on the skin in the elbows one hour prior to blood sample collection. After 15 minutes of supine rest in calm surroundings, blood samples
for different laboratory assays will be obtained in a fixed sequence from antecubital venous puncture. As a general routine, plasma samples will be centrifuged (4 °C, 3500 x g, 15 min) within 30 minutes and frozen at -80 °C until assayed. Also, participants will be instructed to bring a morning spot urine sample in a sterile container. Finally, a hair sample of 2 cm length and 0.5 cm with is obtained from the base of the scull.

Further analyses of the biological material includes

- Hematology and biochemistry routine assays will be performed at the accredited laboratory at Akershus University Hospital, Norway.
- Blood samples for microbiological analyses will be collected in 4 mL EDTA tubes and gel-containing tubes, respectively. Detection of microbial EBV-DNA will be performed by real-time polymerase chain reaction (PCR) in whole blood using a commercial kit (artus EBV, Qiagen, Hilden, Germany). Specific antibody responses will be assessed using anti-EBV EBNA IgG (Bio-Rad, Dreieich, Germany) and anti-EBV VCA IgG and IgM (Hiss Diagnostics, Freiburg, Germany). Also, antibodies against CMV and *Borrelia burgdorferi* will be assayed.
- Blood samples for analyses of plasma catecholamines will be obtained in vacutainer tubes treated with ethylene glycol tetra acetic acid (EGTA)–glutathione, and thereafter subjected to high-performance liquid chromatography (HPLC) with a reversed-phase column and glassy carbon electrochemical detector (Antec, Leyden Deacade II SCC, Zoeterwoude, The Netherlands) using a commercial kit (Chromsystems, München, Germany) (Tsunoda 2006; Hjemdahl 1984).
- For genetic analyses, DNA will be extracted from whole blood; SNPs of candidate genes will be assayed with standard methods (TaqMan). For gene expression analyses, samples will be obtained in PaxGENE tubes and subsequently subjected to quantitative PCR analyses.
- For immune assessment, a broad range of cytokines will be assayed by Luminex microarray in EDTA plasma. Number and cytotoxic function of NK-cells will be assessed applying flow sorting and stimulation of cell cultures. Also, peripheral blood mononuclear cells (PBMC) will be snap frozen, making subsequent molecular analyses feasible.
- Urine samples and hair samples will be subjected to analyses of cortisol.

**Questionnaire**

A questionnaire is distributed to all participants, being composed of the following validated instruments:

- Autonomic Symptom Profile (Suarez 1999), translated and slightly modified.
- Chalder Fatigue Questionnaire (Chalder 1993), translated and validated for a Norwegian population (Loge 1998).
- PedsQL (Varni 2007), translated and validated for a Norwegian population (Reinfjell 2006).
- Functional Disability Inventory (FDI) (Walker 1991), translated and slightly modified
- Brief Pain Inventory (Klepstad 2002)
- Life Event Checklist (LEC) (Johnson 1980)
- Hospital Anxiety and Depression Scale (HADS) (Zigmond 1983)
- Child-Adolescent Perfectionism Scale (CAPS) (Flett 2000)
- Toronto Alexithymia Scale-20 item (TAS-20) (Bagby 1994)
- Brief Illness Perception Questionnaire (BIPQ) (Broadbent 2006)
- Karolinska Sleep Questionnaire (KSQ) (Kecklund 1992)
- The Penn State Worry Questionnaire (Meyer 1990)
Furthermore, there are questions specifically related to the different diagnostic criteria of CFS, including the CDC-criteria (Fukuda 1994), and the Canadian criteria (Carruthers 2003), and simple questions regarding life style and demographics. The questionnaire is completed during the in-hospital investigational day.

The Chalder Fatigue Questionnaire (CFQ) (Chalder 1993) is regarded a valid outcome measure in CFS research among adults (Fukuda 1994; White 2011) as well as adolescents (Godfrey 2009; Tanaka 2008). In this study, the CFQ total sum score is selected as one of the primary endpoints; i.e. the sum across all 11 CFQ items, each of which is scored on a 0-3 Likert scale. Total range is from 0 to 33; higher scores imply more severe fatigue. In addition, dichotomous scores (0 – 0 – 1 – 1) will be used for definition of chronic fatigue caseness; i.e. a sum score of dichotomised responses ≥ 4 (see above).

**Brain fMRI**

Functional neuroradiological assessments by means of fMRI are performed at the Intervention Centre, Rikshospitalet University Hospital, by a whole-body 3-Tesla MRI unit (Philips Medical Systems, Best, The Netherlands). Blood Oxygen Level Dependent-data (BOLD) are used to construct T2-weighted, functional images, whereas T1-weighted images are used for visualization of the relevant anatomical structures (prefrontal cortex, amygdala, locus coeruleus, raphe nuclei). Specially developed software (MRIConvert, MRICroN, SPM) is applied for electronic imaging modification, allowing better definition of anatomical areas, standardization of measurements in accordance with inter-individual variability, and statistical analyses. In order to investigate flexibility and inhibition related to prefrontal cortex, the participants will be instructed to perform simple exercises (‘go/no-go paradigm’). The exercise is developed by our collaborating institution Dept. of Psychology, University of Oslo; it has previously been validated for adolescent CFS/ME patients (Wortinger 2015).

**Qualitative interview**

Interview is one of the most common methods of gathering data in qualitative as well as mixed methods research (Kvale and Brinkmann, 2009). Kvale and Brinkmann make a distinction between unstructured, semi-structured and (fully) structured interviews, and they identify a number of interview questions with specific characteristics and goals: introducing, follow-up, probing, specifying, direct, indirect, structuring and interpreting questions.

In the present study we will use semi-structured interviews prior to the intervention, immediately after the intervention and 1 year after the intervention. The interview consists of two parts: a) It seeks to explore how the patients experience their suffering (CFS/ME) and its influence on their physiological, psychological and social conditions and quality of life, and how they experience the treatment program and its effects on conditions and quality of life. The participants will be invited to tell stories to illustrate or elaborate on selected themes. b) It incorporates an affect consciousness interview (ACI), measuring four different aspects of affect consciousness; attention, tolerance, emotional expressiveness and conceptual/verbal expressiveness of ten basic emotions. These emotions are interest, joy, tenderness/care fear, sadness, anger, contempt, disgust, shame, jealousy and guilt. The interview was originally developed for adults (Monsen 2008). Age-adjusted changes were later made in the interview and rating system for use with children and adolescent (Taarvig 2014). An interview guide for the child version is available, which has satisfactory reliability and validity.

The interview will be analysed using systematic text condensation, as modified by Kirsti Malterud (2003, p. 99), inspired by Giorgi’s phenomenological approach.

**Physical activity**
Accelerometers are widely used devices for accurate measurements of physical activity (Ward 2005). They provide reliable and valid data among patients with impaired physical capacity (Macko 2002), and have been successfully applied in previous CFS studies (Meeus 2011; Evering 2011).

In this study, we will use the activPAL accelerometer device (PAL Technologies Ltd, Glasgow, Scotland) for monitoring of daily physical activity during seven consecutive days. ActivPAL provides reliable and valid data on step number and cadence as well as time spent on walking, standing and sitting/lying during everyday activities (Grant 2006; Ryan 2006). The device has also been validated in an adolescent population (Dowd 2012), and it is sensitive for changes of step number with time (Dahlgren 2010).

A recording period of seven consecutive days is selected, according to present recommendation (Ward 2005). The recording unit (weight: 15 grams, size: 53 x 35 x 7 mm), will be attached midline on the anterior aspect of the thigh by specially designed adhesive strips (PALstickies), according to the manufacturer’s instruction. The participants will be instructed to wear the unit permanently (ie, also during the night); however, they will be shown how to remove it during showering/bathing and re-apply it afterwards. After the recording period, the unit will be returned by mail in a pre-stamped envelope.

Data from the recording units is transferred to a computer running producer developed software. For each participant, all recording epochs will be carefully and independently reviewed. If one recording day is considered to contain erroneous or incomplete data, that entire day will be removed from further calculation. Finally, the mean number of steps per day will be calculated for all recording epochs. The mean number of steps per day is the primary endpoint in this study.

**Randomizing and blinding**
Patients are randomized to either mental therapy or routine follow-up by the general practitioner (GP) in a 1:1 probability. A computer-based routine for block randomization is provided by the Dept. of Research Support at the Norwegian University of Science and Technology, Trondheim. The program is operated by a research nurse who is not otherwise affiliated with the study. It is not possible to blind patients or therapists for group allocation. However, both patients and therapist will be blinded for end-point evaluation. In order to reduce variability of procedures, as few persons as possible are to be involved in the practical patient work.

**Intervention – the mental training program**
The intervention consists of one introductory group session (up to 5 patients and their parents/next-of-kin), 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 3). 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), ‘trick into action’
- Cognitive challenges: Challenging thoughts about disease process, stimulus and outcome expectancies, prognosis

A detailed treatment manual has been developed (ref. manual).
Effect monitoring
The patients are thoroughly assessed at week 12 by an investigational program identical to the one performed at inclusion. The primary end-point is mean steps/day count during one week. Secondary end-points are:

- Biomarkers
  - Plasma catecholamines
  - Urine cortisol/creatinine ratio
  - Cytokine network
  - Number of NK-cells
  - Plasma gene expression profiles
- Autonomic cardiovascular control
  - Supine heart rate (HR) and heart rate variability (HRV)
  - HRV during fixed breathing rate
  - HR and blood pressure responses to upright posture
- Cognitions/neurobiology
  - Working memory (digit span test)
  - Cognitive inhibition (color-word interference test, condition 3)
  - Salience network connectivity (brain fMRI)
- Symptoms/function
  - 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

Side effects and unexpected events
A separate questionnaire addressing possible side effect, unexpected events, complication etc. related to the mental intervention is to be 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.

Statistical analyses
The ‘full analysis set’ is defined as all patients who were randomized to mental intervention/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.

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.

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 ≤ 0.05 is considered statistically significant. No correction for multiple comparisons will be applied. For statistical tests of intervention outcome (cf below), variables having a skewed distribution will be transformed in order to achieve a normal distribution.

Intention-to-treat analyses (full analysis set) will be used to compare the group allocated to mental intervention 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 calculated 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.

Translational aspects
This study explores a mental training program in a patient group that is thoroughly characterized in terms of basic laboratory sciences (microbiology; molecular genetics; endocrinology; immunology), applied physiology and psychology (cardiovascular assessment; cognitive testing) and clinical methods (questionnaire; activity recordings) in an attempt to explore a common clinical problem (adolescent chronic fatigue after EBV infection). Thus, the translation element is strong.

Ethical considerations
Participation is based upon informed consent, and thorough information will be provided orally as well as in writing to the participants and (if younger than 16 years) to their parents/next-of-kin. All data will be treated and stored without personal identifying information, and in accordance with national directives. Approbation will be sought from the Regional Committee for Ethics in Medical Research and the Norwegian Data Inspectorate. The study will be registered at ClinicalTrials.gov, and will adhere to the CONSORT statement.
Venous puncture might be painful; therefore, an ointment containing the local anaesthetic lidocaine (Emla®) is routinely given as a prophylactic. Other investigational methods applied in this study are neither painful nor harmful. Each participant will receive a gift certificate having the value of NOK 200 after each completed in-hospital assessment.

CBT is not associated with any harmful effect in CFS/ME, as recently reported from the PACE trial (Dougall et al. 2014). Thus, we do not assume any harmful effect of the mental intervention in the present study. Still, possible side effects and complications will be thoroughly monitored; if such occur, they will be described in detail in the patient’s specific study files and in the ordinary hospital record, and reported in scientific publications. In case of a serious adverse event, the patient will be considered excluded from the intervention trial.

**Research group and collaboration**

The principal investigator of this study (Prof. Wyller) has for ten years been a leading CFS/ME researcher. He is responsible for the NorCAPITAL and CEBA projects on adolescent CFS/ME, and heads the research group PAEDIA at Akershus University Hospital. The group possesses competence in clinical trials and epidemiology as well as experimental methods, and has extensive local, national and international collaboration. Prof. Wyller is also an associated member of the research group INTERPRET (OUS Rikshospitalet) on childhood cancer, and participates in two international research networks: BAKOPP (on late effects after childhood cancer) and CauseHealth (on causation theory in the medical sciences)

Within CEBA, collaboration with a large group of researchers has been established. This collaboration will be prolonged in the present study.

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Progression and finances

In the prospective part of CEBA, patient inclusion commenced March 1, 2015; thus patients might be eligible for inclusion in the present study 6 months later, i.e. from Sept. 1 2015. The prospective part of CEBA is assumed to use 1 year for inclusion of the entire patient material. As the intervention period in the present study last for 3 months, we expect study completion by December 2016. Publication of the main results is to be expected in 2017. The project will be completed by 2018.

One PhD-student (full time) will be affiliated with the project. We will apply for funding for this PhD-student from external funding bodies, such as the Health South-East research grants. The PhD-student will be responsible for statistical analyses and writing of scientific papers, closely supervised by the principal investigator and other collaborators. Also, the PhD-student will participate in data collection. All laboratory analyses will be carried out by the collaborative laboratories. The expenses of these analyses, as well as expenses related to equipment, therapists etc., are covered from previous grants.

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<td>One PhD-student, 100 % employed</td>
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Publishing

Results from this project will be published in international, peer-reviewed medical journal and constitute the basis for one PhD-dissertation. The most important results will be offered to clinical journals of high impact. We will also report negative results. Co-authorship will be granted according to the Vancouver guidelines. The following scholarly papers might be anticipated:

- The clinical effect of an individually tailored, multidisciplinary mental training program to adolescents suffering from CFS/ME after EBV-infection
- Mental training in adolescent CFS/ME: effects on catecholamines and HPA axis function
- Changes in brain salient network connectivity after mental training in adolescent CFS/ME: implications for models of disease mechanisms
- Mediators of the clinical effect of mental training in adolescent CFS/ME: the role of worrying and affect consciousness.
- Associations between clinical improvement and alteration of autonomic cardiovascular control after a mental training program in adolescent CFS/ME

In addition, the following means of dissemination will be considered:

- Participation in CFS conferences as well as general scientific conferences
- Review papers in international and national journals
- The activity provided by the recently established Centre of Competance for CFS at OUS (information leaflets, supervision, conferences, etc.)
- Direct contact with all participants in this project.
• Communication with two national patients’ organizations for CFS/ME (Norges ME-forening og MENiN).
• Participation in the official CFS network headed by the Norwegian Health Directorate
• Articles and interviews in the mass media and social media

5. Research group
The PAEDIA research group
The aim of the PAEDIA research group is to initiate and execute clinical and translational research within the field of Pediatrics, particularly focusing on areas that would benefit from an integrated, multidisciplinary approach (http://www.med.uio.no/klinmed/forsking/grupper/paedia/index.html). At present, the group conducts three large research projects: NorCAPITAL (on disease mechanisms and treatment in chronic fatigue syndrome), CEBA (on late effects after acute Ebstein-Barr virus infection) and AcceHEART (on cardiovascular autonomic control after cardiac transplantation). The group possesses competence in clinical trials and epidemiology as well as experimental methods related to cardiovascular physiology.

PAEDIA was founded in 2014, and consists at present of 1 professor, 7 PhD-students, 4 students at the master level and 1 secretary. The group is headed by professor Vegard Bruun Wyller.

Research networks and supervision capacity
PAEDIA has extensive collaboration with local, national and international research group, established through NorCAPITAL, CEBA and other projects. PAEDIA participates in two research networks: BAKOPP (on late effects after childhood cancer) and CauseHealth (on causation theory in the medical sciences). Prof. Wyller has been a leader and is at present an associated member of the research group INTERPRET at OUS Rikshospitalet.

Two PhD-students in PAEDIA are to defend their PhD-thesis during spring 2015. Thus, supervision capacity will be available for the present project.

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