PROTOCOL for the RESEARCHER PROJECT:

DEEP BRAIN STIMULATION FOR DISABLING ACTION TREMOR: A CONTROLLED COMPARISON OF TWO DIFFERENT TARGETS

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1. Principal goal of the study.

The principal goal of this study is to improve the efficacy of deep brain stimulation (DBS) as treatment for disabling action tremor of the arms, the most common form of involuntary movement disorder in both younger and more elderly adults (1). With increasing severity, action tremor impairs many important activities of daily living, can render affected individuals unable to work, and can lead to complete dependence on assistance from others. Efficacy of medical treatment for this condition is very limited and often unsuccessful. In severe cases DBS is the only potentially effective treatment (2). DBS of the thalamic nucleus Ventralis Intermedius (VIM) has traditionally been used, but the posterior subthalamic area (PSA) has been suggested recently as a better target, leading to more complete and sustained tremor-suppression. More complex types of action tremor have also been successfully treated using the PSA. However, controlled and comparative studies of the two targets are lacking, and have been called for by world-leading tremor experts (2, 3).

The Departments of Neurology and Neurosurgery at Oslo University Hospital (OUH), together with the corresponding departments at St Olav's Hospital in Trondheim, have been given the national task to provide DBS treatment to the Norwegian population. From the outset, this study was therefore planned as a multi-center study, with both OUH and St Olav´s hospital as including centers, and with international collaboration with a world leading German DBS center (University Clinic Wuerzburg/headed by professor Jens Volkmann) - to perform the first double-blind, randomized, controlled , comparative study of VIM- versus PSA-DBS in disabling action tremor. However, St Olavs Hospital withdrew their consent to participate before inclusion was started.

Therefore, Oslo University Hospital has been the only center including patients since inclusion was started in April 2014. Inclusion was closed in December 2018, with 45 patients included. The collaboration also includes the Western Health Region, so that patients will be recruited from all health-regions of Norway.
Clinical efficacy and safety will be related to precise stimulus location, assessed by fusion of preoperative MRIand postoperative CT. Neuropsychological testing will elucidate whether cognitive functions are altered.

This study will allow us to determine which DBS target provides the best and most sustained suppression of action tremors. Improved efficacy will greatly enhance the function and well-being of many patients, improve their work-participation and reduce their need for assistance in daily-life activities, and thus increase the cost-effectiveness of this resource-demanding therapy.

2. Aspects relating to the research project

2.1. Background and status of knowledge

Tremor is defined as rhythmic and oscillating involuntary movements of a body part. *Action tremor* occurs when a body part is activated, and is clinically most frequently seen in Essential (idiopathic) Tremor (ET), with an overall prevalence of 0.9 %, and of 4.6 % in people over 65 years (1). But it can also be the most disabling symptom in many other neurological diseases such as dystonia, multiple sclerosis (MS), advanced Parkinson's disease (PD), and some spino-cerebellar ataxias.

Relevant physiology and anatomy

The basic *normal* physiological mechanisms that underlie tremor are central neurogenic oscillations, spinal and supraspinal reflex oscillations, and peripheral mechanical oscillations. *Central neurogenic pathological tremors* emerge from disruptions of central neural networks involving pathways from spinal cord to cerebellum, from cerebellum via brainstem to thalamus, and thalamo-cortical loops via the basal ganglia. Simultaneous recordings of EMG (electromyography), EEG (electroencephalography), and MEG (magnetoencephalography) have demonstrated the involvement of ipsilateral cerebellum, contralateral thalamus and sensorimotor cortex in ET, Parkinson, and several other tremor types. Thus, the cerebello-thalamo-cortical pathway is probably involved in all tremors (4). The exact mechanisms that disrupt these pathways and produce pathological oscillations in the various tremor conditions remain, however, largely unknown.
The cerebello-thalamic tract originates from the cerebellar nuclei (dentate, emboliform and globose), ascends and crosses in the pons and enters the *red nucleus* (RN). Most fibers project further to the *ventral thalamic nuclei - oralis* (VO) *and intermedius* **(VIM)**. The RN lies in the mesencephalon, medial and ventral to the subthalamic nucleus (STN). The *posterior subthalamic area* **(PSA)** is the region inferior to VO and VIM, dorsal and posterior to STN, and lateral to RN. Its principal components are the nucleus called Zona Incerta (ZI) and the fibre bundle called the prelemniscal radiation (RaPrl). The important descending motor pathway (pyramidal tract) lies laterally and the important ascending sensory pathway (medial lemniscus) lies posteriorly to PSA. Whereas STN and RN are visible on standard T2-weighted MRI-scans, PSA is only indirectly defined by these surrounding structures. A study using diffusion-tensor imaging (DTI) and fiber tracking has, however, shown that DTI can potentially differentiate between the fiber tracts passing through this area, and thus can greatly improve assessment of the anatomical structures affected by the current from an implanted DBS electrode (11).

Classification and differential diagnosis of action tremor disorders
This can be difficult, since with rare exceptions there are no confirmative diagnostic tests or biomarkers for the primary tremor forms. Differential diagnosis of primary action tremor forms such as ET, Dystonic tremor (DT) and Cerebellar tremor (CbT), therefore relies mainly on clinical examination and the exclusion of underlying diseases causing secondary action tremors (such as PD and MS) by supplementary imaging and other lab tests. Action tremor is divided into *postural* (when a position is maintained), or *kinetic* (when a movement is made). Other neurological findings (dystonia, cerebellar, pyramidal, parkinsonian, neuropathic signs), and systemic signs must be assessed. Age at onset, associated disease, medication history/response, response to alcohol, possible drug abuse and family history of neurological disease (especially tremor) must be assessed.
- ET. Mainly a bilateral, largely symmetric postural or kinetic tremor involving the hands and forearms. Additional or (rarely) isolated head tremor may occur, but no abnormal posturing. Other causes of primary or secondary tremor forms must be excluded (5).
- DT. Strongly supportive of DT are other signs of dystonia (abnormal posturing and frank, involuntary dystonic movements). Suggestible, softer signs are asymmetrical and irregular or jerky limb tremor, atypical rest tremor, and position-or task-specific tremor.
- CbT. For this diagnosis, there must be a pure or dominant intention tremor of the extremities, uni- or bilateral, with a frequency mainly below 5 Hz. Postural tremor may be present, but no rest tremor. If only postural tremor is present, other clear cerebellar signs must be present to classify the tremor as cerebellar. So-called titubation of the head or trunk is a slow-frequency oscillation in the erect positon that is also thought to be of cerebellar origin.
- Holmes tremor. Rest- and intention tremor, +/- postural, frequency usually < 5 Hz, often associated with a lesion of the brain stem, cerebellum or thalamus
- Neuropathic tremor. Postural or kinetic tremor of limb(s) affected by a peripheral neuropathy.

Supplementary diagnostic workup

- MRI is obligatory in all tremor cases to show/exclude tremor-causing lesions such as infarcts, MS plaques or other inflammatory diseases, cerebellar atrophy, or atrophy or pathological signal changes along the cerebello-thalamo-cortical circuits, including the basal ganglia.
- DAT-scan/^{131}I-FP-CIT SPECT of the DopAmine Transporter (DAT) shows reduced binding in the striatum in PD and other degenerative parkinsonisms, but not in ET, DT or CbT.
- Laboratory tests. Blood (+/- CSF and urine) to exclude hyperthyreosis, electrolyte disturbances, metals (iron, copper), hyper/hypoglycemia, vitamin B12 deficiency, hepatic or kidney diseases.

Treatment of primary action tremor disorders

I. Medical treatment. As neither the molecular or neurotransmitter deficits or the mechanisms of the pathological oscillations are known, medications used are only symptomatic. The two most commonly used drugs for ET, the non-selective beta-blocker propranolol and the anticonvulsant primidone, both received a level A recommendation of efficacy by the American Academy of Neurology in 2005. This was based on mostly small and short-term studies (3-6 weeks), showing an average tremor reduction of about 50-60% in about 50% of patients (2). No controlled long-term studies have been done, but open-label studies indicate development of tolerance and reduced effect in 10-15%. Level B evidence of a probable effect has been given to other beta-blockers (atenolol, sotalol) and the antiepileptics alprazolam, topiramate and gabapentin. None of these has been shown to be more efficaceous than propranolol or primidone (2). Unfortunately, among the many drugs tested, even those with established efficacy for ET provide only partial relief in a subgroup of patients. There have been no systematic studies for other tremors like dystonic or cerebellar tremors (4). Thus, for these patients no medications with established efficacy exist, except intramuscular botulinum toxin injections for dystonic head tremor (2).

II. Deep brain stimulation (DBS)

i. Stimulation of VIM. DBS of the Nucleus Ventralis Intermedius of the thalamus (VIM) has long been available, and VIM has been considered the target of choice for patients with disabling action tremor at most centers, including ours. Open-label, mostly short-term studies of VIM-DBS in ET have reported up to 80-90% reduction of action tremor, but long-term clinical experience and studies show that gradual loss of tremor control over months and years occurs in many patients (2,6). Masked raters were not used (2), except for one study (7). Several studies did not differentiate between efficacy on postural versus kinetic tremor. Of those that did, 2 of 3 showed a reduced efficacy on kinetic tremor in the long-term (6,8). This problem, termed ”development of tolerance” to the stimulation, is emphasized in recent reviews (2,3) and clearly limits the functional long-term benefit of VIM-DBS. Whether this is due to tolerance to the stimulation, progression of the underlying disease process, or suboptimal electrode placement is under debate. Although reduced tremor control often can be corrected by increasing the current, this effect is only temporary or leads to intolerable side-effects. VIM-DBS is also limited by being less effective on proximal tremor, which is often the most invalidizing symptom.

Because VIM cannot be seen on MRI or mapped using microelectrode recordings, targeting it employs the use of standard stereotaxic coordinates. The definition of these varies between centers. They are defined in relation to the intercommissural line (ICL) between anterior and posterior commissures. Final placement of the electrode is decided only after peroperative clinical testing of effect on tremor and side effects in the awake patient. Thus, the cooperability of the patient and the skills of the neurologist performing peroperative testing are crucial. Bilateral VIM-stimulation is associated with a relatively high rate of side effects. In a meta-analysis of 430 patients, 19 % had paresthesias, 9 % dysarthria, 7 % headache and 6 % unsteadiness or gait difficulties. Therefore, many centers offer only unilateral stimulation to most patients even if they have bilateral tremor.

ii. Stimulation of PSA. The limitations of VIM-stimulation have led to a renewed interest in exploring the PSA as an alternative. Open label case series from several centers indicate better results from PSA-DBS than VIM-DBS (9,10,11,12), particularly in reducing kinetic tremor, including proximal arm tremor and intention tremor. The targeted area within the PSA varies

among centers. Kitagawa et al published a dramatic response to PSA-DBS in two patients with severe proximal arm tremor, one with ET and one with DT (13) and similar results in 8 patients with ET and proximal arm tremor (9). Average tremor reduction was 81%, sustained during median 22 months of follow-up, with low current consumption. Comparison of stimulation efficacy for electrodes in VIM versus PSA favoured the latter. Stimulation in the Zona Incerta (ZI) or the prelemniscal radiation (Raprl) were both effective, and side-effects were reported to be mild and transient. Plaha et al (11) reported results from blinded 1-year follow-up of bilateral stimulation of the caudal ZI in 5 patients with PD tremor, and 13 patients with action tremors from a range of diseases (ET, MS, CbT, DT, Holmes tremor). The target was slightly lateral to that of Murata et al (for comparison, see ref 11). Average improvement of postural/action tremor was 88% and of rest tremor 95%. In the MS-patients, both severe proximal arm tremor, truncal ataxia and severe head-and-neck tremor improved. There was no significant decline of clinical efficacy or significant change in stimulation parameters during serial follow-ups, but some side-effects were seen in a few patients due to misplaced electrodes or edema. Blomstedt et al reported results of PSA-DBS in 21 patients with ET (most unilateral), achieving on average 95% tremor reduction and 87% functional improvement in the contralateral arm (12). Transient, mild expressive dysphasia was observed in eight patients. In summary, the most frequent side-effects reported in PSA-DBS series are paresthesias, dysarthria, dysequilibrium and blurred vision, and thus similar to those observed with VIM-DBS, but are consistently reported to be mild and transient in almost all patients. No controlled comparison of efficacy and safety between the two targets have been reported so far. With respect to the ICL, the targets used in the above studies were 10-14 mm lateral, 6-7.5 mm posterior to midpoint, and 2-4 mm inferior. Few authors have studied different targets in the same patients. Herzog et al compared stimulating with the upper electrode contacts the thalamic level, and with the lower contacts 1.5mm below the ICL in 21 patients with ETor MS-tremor. The results favoured the contacts below the ICL (14).
In 2010, Coenen et al presented their use of DTI and fiber tracking to determine the exact location of the most effective electrode contact placed in the subthalamic area in a unilateral PD tremor patient. They concluded that effective stimulation was achieved by a contact that stimulated the dentato-rubro-thalamic tract (DRT) as this crosses the subthalamic area (15). In 2011 the same group published successful DBS in a patient with head-tremor, using visualization of the DRT by DTI-MRI for direct targeting (16, Figure 1).

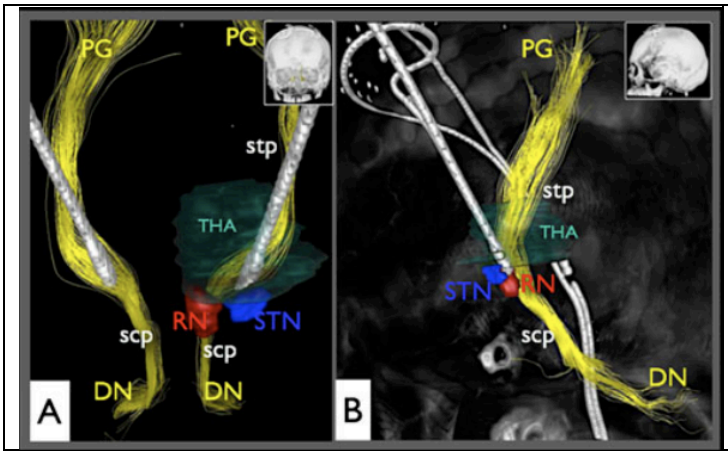

Figure 1. Shows DBS electrode positions in relation to fiber tracts in the thalamic and subthalamic area in a patient with tremor, using helical CT merged with diffusion tension MRI/ fiber tracking. (STN= subthalamic nucleus, RN= red nucleus, THA= thalamus, DN= dentate nucleus, scp= superior cerebellar peduncle, stp= superior thalamic radiation)
From Coenen et al, Acta Neurochir 2011 (ref.16)

Fluoro-Deoxy-Glucose Positron Emission Tomography (FDG-PET) and Neuropsychological assessment. FDG-PET was used in a recent study to define a metabolic pattern of PD tremor characterized by covarying increases in the activity of the cerebellum/dentate nucleus and primary motor cortex, and, to a lesser degree, the caudate/putamen. VIM-DBS resulted in consistent reductions in pattern expression. The findings suggest that PD tremor is mediated by a distinct metabolic network, involving primarily cerebello-thalamo-cortical pathways in which effective reduction of activity is associated with significant diminution of tremor (17). No similar study has

so far assessed this in other tremor forms, or after PSA-DBS. We therefore wanted to perform FDG-PET at baseline and at 1 year of DBS, but we could not manage the costs of this procedure, and it was therefore omitted.
Possible impact on cognitive function has not been assessed in published studies of PSA-DBS. It cannot be excluded, however, that PSA-DBS or VIM-DBS could have an impact on some aspects of cognitive function. We will therefore perform a standard neuropsychological test battery in all patients before and at 1-year follow-up.

2.2. Approaches, hypotheses and choice of method

To overcome the limitations of today´s standard method of treating severe action tremors with VIM-DBS, we will now collaborate with one of the world's leading DBS experts (Jens Volkmann, Germany), to perform the first double-blind, randomized, controlled and comparative study of VIM-DBS versus PSA-DBS in patients with disabling action tremor. This will entail an interdisciplinary approach that combines cutting edge neurosurgical intervention, neurophysiological manipulation, brain imaging, and neurological and neuropsychiatric assessment. In combination, these methods will provide novel insight into the design of DBS for action tremor, and help provide a platform in Norway and internationally for making similar advances in the use of DBS as a therapeutic tool for other neurological disorders.

We will implant one quadripolar (or octapolar) electrode so that it covers both targets on one side, unilaterally or bilaterally as indicated clinically. The efficacy of stimulating each target will be studied in individual patients and between patient groups in a cross-over design, in two consecutive 3-month periods, by the use of validated tremor scores. Further continuous stimulation of the most effective target in each patient will be evaluated after another 6 months. This will provide unbiased efficacy-data about the two targets, both within each patient, and between patient groups. Stimulation efficacy will also be evaluated in relation to the exact target localization, defined by merging post-op helical CT scan (shows the four electrode contacts), with pre-op MRI (the MRI protocol includes DTI uptake for fiber tracking.) Such high-resolution correlation data has to date only been published in a few action tremor patients world-wide, and will add extremely important new data to aid DBS targeting in the future. Since little is known about whether cognitive functions are altered by the disease or the treatment, we will perform neuropsychological testing before and after effective DBS treatment.

I. Study overview.

- Study design: Single-center, prospective, randomized, double-blind. Cross-over.
- Number of patients to be included: Minimum 44.
- Inclusion criteria: Patients of both genders aged 18 – 80 years. Min 5-yr duration chronic action tremor of upper limb(s), w/ or w/out tremor of head/neck, trunk, lower limbs, who have insufficient relief from adequate trials of recommended medications. The arm tremor must be so severe that it interferes with the patient's work performance or activities of daily living, such as drinking/eating, dressing/hygiene, and/or writing. Clinical diagnosis (according to criteria defined by the Consensus Statement of the Movement Disorders Society (5)) include ET, DT, CbT- idiopathic or secondary (to e.g.MS or SCA), or severe PD tremor (who are not eligible for DBS of the subthalamic nucleus). A new clinical classification of tremor syndromes published in 2018 will also be used to support/update the clinical classification of the study population (18).
- Exclusion criteria: Brain MRI showing so marked general atrophy, or supra-tentorial white matter changes, that the safety of the procedure is affected. Co-morbidity of dementia or other severe neuropsychiatric disorder (major depression or anxiety disorder, active/recent psychosis, drug or other substance abuse). Increased risk of bleeding, cancer at advanced/not stabilized stage, other co-morbidity with short life expectancy. Other surgical contraindications.
- Identification of the surgical target: The quadripolar electrode will be placed so that each target (VIM and PSA) is covered by at least one of four electrode contacts. The targets will be found using

preoperative MRI (3 Tesla) merged with helical/3D CT, according to predefined coordinates, refined by relation to neighboring MRI-visible structures (STN and RN). Electrode trajectories will be defined to avoid cerebral sulci, vessels and ventricles.
- Primary endpoints: 1) The difference in the change from baseline to the end of each of the two 3-month cross-over periods in *the objectively observed tremor of the contralateral upper limb(s)*, as evaluated by items 5 (right)/6 (left),10 (for dominant hand only), and 11-14, in the Fahn-Tolosa-Marin (FTM)-score (19), with VIM- versus PSA-stimulation. *Functional disability of arm tremor* (items 16-21) is also part of the primary endpoint evaluation.
2) The difference in the change from baseline to the end of each of the two 3-month cross-over periods in the items scoring tremor of face/tongue/voice/trunk/lower limb(s), with VIM- versus PSA-stimulation.
The exact brain area stimulated in each patient will be radiologically evaluated by the pre-op MRI merged with a post-op helical CT-scan. These images are exported via CD´s to the soft-ware SureTune (Medtronic), to show the localization of the implanted electrodes (and the active contacts used) on the patient´s brain anatomy. This work is done using the Visual Lab portifolio developed at the University Clinic Wuerzburg by Jens Volkmann and Martin M. Reich (see 2.3.), and is supervised by them.

- Secondary endpoints: 1) Change from baseline to 1-yr, with stimulation at the most optimal of 4 electrode contacts of each patient (selected after the second randomization period), of the total FTM-score, tremor of the upper limb(s) (same items as above) and of the items scoring tremor in the face, tongue, voice, trunk, lower limb(s). 2) Change from baseline to 1-yr of Quality of Life in Essential Tremor (QUEST) scale, and Visual Analogue Scale of Global Disease Burden as assessed by the patient. 3) Frequency and severity of adverse events (surgical complications and stimulation related side-effects), including eventual deterioration on neuropsychological testing from baseline to 1-yr of stimulation.

II. Methods
i) Clinical evaluation and scoring. Before the patients are invited to participate, they have been thoroughly evaluated for correct diagnosis, including a complete clinical neurological examination, MRI of the head/brain (+/- spine/spinal cord), laboratory tests, etc. *The inclusion examination* ensures that inclusion criteria are fulfilled and that none of the exclusion criteria are met.

The study examinations include clinical examination and scoring as shown in the table:

	Baseline	1. Random.per./3 mo.	2. Random.per./6 mo.	1 year
FTM-tremor scale*	X	X	X	X
Neurological exam.	X			X
QUEST	X	X	X	X
Adverse events reg.		X	X	X
Neuropsych.exam.	X			X
Video recording	X	X	X	X

- *The Fahn-Tolosa-Marin tremor scale* contains 21 items scored 0-4, with 0 indicating no tremor/disability and 4 severe tremor (constant, high amplitude)/inability to perform a task due to tremor. Item 1-9 score tremor for face, tongue, voice, head, trunk and the four extremeties. For face only rest tremor is scored, for tongue, head and trunk rest and postural tremor, and for the extremeties action/intention tremor is also scored. Items 10-13 test handwriting (for dominant hand only), and spiral drawing with right and left hand, and line drawing between defined points. Item 14 tests pouring of water from one plastic cup to the other. Item 15-21 describe functional disability of speaking, feeding (not liquids), bringing liquids to mouth, hygiene, dressing, writing, working.
- A video recording of the objectively tested items of the FTM was not originally planned from the ouset, but we realized it was useful and has been performed from patient # primarily to document

the phenomenology of tremor at baseline and of resttremor at follow-up. All patients have given their oral consent to these video recordings. Written consent will be collected before these video recordings are actively used to support data analysis.
- *Quantification of tremor using an electronic device carried on the patient´s wrist, such as the* Actiwatch™ (actigraph) was originally planned to be part of the tremor evaluation. But these device-based measurements was not performed in this study, as they became too expensive.
- *Quality of life in Essential Tremor- scale (QUEST).* A 30 item questionnaire developed specifically for tremor patients, evaluating quality of life, cognitive, and emotional aspects of the tremor (20).
-*VAS of Global Disease Burden (patient evaluated) and of tremor related pain.* Visual analogue 0-10 centimeter continuous scale, on which the patient scores at which severity they assess the global tremor disease burden and tremor related pain.

ii) Operation. Preoperative axial MRI sequences (T2-weighted fast-spin-echo, diffusion-weighted spin-echo echo-planar imaging, and 3D inversion prepared T1-weighted gradient-echo) will be obtained on a 3 Tesla MRI-scanner the day before the operation. In local anaesthesia a CRW™ stereotactic frame, (Radionics, MA, USA) is mounted, placed parallell to the AC-PC line, before performing a stereotactic 3D CT scan. The MRI and CT scans are merged using the iPlan™ (version 3.0) computer-aided neuronavigation system (BrainLAB, München, Germany), or updated versions, which is also used to plan the targets based on predefined stereotactic coordinates for VIM and PSA, refined according to relationship to the MRI-visible STN and RN. Trajectory angle will be chosen to cover VIM and to enter PSA slightly posterior and medial to STN, at the level of maximal diameter of RN. To ensure safety, trajectories are always planned to avoid vessels, sulci and ventricles. If the trajectory angle needed to reach both targets is judged to compromise safety, the trajectory is adjusted so that the PSA is still reached, and as close to the preferred VIM-target as possible.
Microelectrode recordings (MER) were not performed. This was decided prior to inclusion of the first patient.
Clinical test stimulation is performed in the awake patient on the implanted permanent quadripolar electrode (model 3389 or 3387, Medtronic, MN, USA, or Boston Scientific Cartesia electrode), at 4 levels, corresponding to the four levels of the electrode contacts (for both the Medtronic and the Boston electrode, each electrode level spans 1,5 mm, with 0,5 mm spacing between electrodes). This should confirm good tremor suppression and no unaccepatable side effects, otherwise a second trajectory is chosen, based on anatomical considerations to improve effect on tremor, or avoid the unacceptable side-effects.
Electrode position is checked using perioperative radiography, and the electrodes fixed to the scull. After removal of the stereotactic frame, the electrodes are connected to a dual pulsegenerator (Activa PC or RC, Medtronic, or Gevia, Boston Scientific) implanted in the subclavicular region.

iii) Randomization periods/stimulation treatment. Half the patients are randomized to receive VIM-stimulation from 0-3 months after surgery and then switched to receive PSA-stimulation for the next 3 months, and the other half to receive PSA-stimulation the first three months and VIM-stimulation the next 3. During these two randomization periods the pulse width will be 60 microsec and frequency 130-145 Hz, monopolar and ring-stimulation mode (bipolar mode only if monopolar leads to intolerable side effects). Current should not exceed 3 mA during the randomization periods. After scoring at the end of the last 3-month randomization period, the electrode contact yielding the best tremor reduction with no or only minor/possible side effects is chosen for further treatment. During follow-up to 1-yr post-op there may be 2 additional visits for optimal adjustment of stimulation parameters. This protocol may be deviated from only if the above limitations clearly provide the patient with unsatisfactory treatment results.

Randomization: Stratified block randomization, performed by a secured web-based service (provided by The Norwegian University of Science and Technology, Trondheim, Norway (http://webcrf3.medisin.ntnu.no). The project leader enters each new patient for randomization after inclusion and operation/implantation of the DBS-system.

iv) Neuropsychological examinations. A standard set of well-known and validated neuropsychological tests will be performed pre-op and 1-yr post-op.

v) ^{18} Fluoro-deoxy-glucose-PET (FDG-PET). This could not be performed due to too high costs.

vi) Imaging analysis to show anatomical position of implanted electrodes/active contacts. The pre-op MRI and a post-op helical CT-scan are exported via CD´s to the soft-ware SureTune (Medtronic), to show the localization of the implanted electrodes (and the active contacts used) on the patient´s brain anatomy, as visualized by MRI. This work is done using the Visual Lab portifolio developed by the University Clinic Wuerzburg by Jens Volkmann and Martin M. Reich (see 2.3.), and is supervised by them.

vii) **Long-term, open follow-up extension.** All participating patients who complete the first year of the study will be invited to participate in an open, long-term follow-up study. Study examinations will be performed at 2 years and 3, 5, 7,5 and 10 years after the operation. The FTM-tremor score, neurological examination, the QUEST quality of life-questionnaire and the HAD-questionnaire will be performed. The TETRAS score will be performed in a subset of patients in whom this score was also obtained at baseline.

viii) **Power calculation and plan for statistical analyses,** Based on earlier research on deep brain stimulation in VIM and PSA for tremor, we assume a mean change (improvement) from baseline to the end of the two randomized 3 months treatment periods of 16 points (standard deviation SD=5) in our primary endpoint (composite FTM-tremorscore of contralateral arm). (Power calculation is done for dominant arm). We defined a clinically significant difference as 1.8 points between the two interventions. Furthermore, we assume a SD of differences of 4. When the sample size in each period is 41 and the number of subjects for each intervention is equal, this 2x2 cross-over design will have 80% power to detect a difference in mean change between interventions of 1.8 points using a paired t-test. In order to account for potential drop-out and missing data, 45 patients will be randomized.

Continuous and categorical data will be described with mean (SD) and number of observations (percentage), respectively. A basic statistical analysis of the 2x2 cross over design assumes no period (systematic difference between periods) and carry over (systematic difference between orders of received interventions) effect. We will assess period effect by comparing the mean response of the two periods using a paired t-test and carry over effect by comparing the mean response of the two orders of received interventions using an independent t-test. If the tests for period and carry over effects are non-significant, these effects are considered absent. Thus, a paired t-test of treatment difference gives an estimate of the treatment effect with 95% confidence interval and p-value.

In addition, we will conduct a linear mixed model approach using a random intercept with maximum likelihood estimation to account for within-subject correlations and fixed effects for treatment, period, and carry-over (interaction between period and treatment). If the period and carry over effect are non-significant, we will re-estimate the mixed model omitting these terms. If the period or carry over effect is significant, we will re-estimate the mixed model analysis including respective significant terms and report treatment effect with 95% confidence interval and p-value adjusted for period or carry over effect. With no missing data or drop-outs, the t-test and mixed

model approach should give equal results. In case of missing data, drop-outs or discrepancy between the t-test and mixed model approach, the mixed model approach will be our conclusive analysis. A p-value < 0.05 is statistically significant.

2.3. The project plan, project management, organisation and cooperation

The project is carried out on the basis of a well established, collaborative network anchored at the Depts of Neurology, Neurosurgery and Neuroradiology at OUS-Rikshospitalet, which includes a long-standing international collaboration with professor Jens Volkmann, University Clinic of Wuerzburg, Germany, a world-leading DBS expert, and his German DBS study group. Professor Volkmann will serve as a senior scientific consultant of the study, and lead the collaborating team at the University Clinic of Wuerzburg, Germany. They have not included patients at their site, but has an important role in providing their well established work-flow for the imaging data analyses necessary to localise the exact position of the active electrode contact (; *de facto* stimulation-site) used at 3 months, 6 months and 1 year follow-up, and if changed thereafter, also after the 1 year follow-up. This work is carried out at their Visual DBS Lab, lead/supervised by junior group leader Martin M. Reich, MDPhD (see also 2.2, I.)

Nationally, the other DBS-centre at St Olavs Hospital (patients from Mid- and North-Norway), was planned to be the third centre performing operations/study evaluations/imaging, but they withdrew their consent to participate before inclusion of patients was started. This was because they concluded at that point that they did not have the necessary personnel resources to participate. The Western Health region and regional collaborators in South-East health regions will contribute/has contributed as planned in recruiting patients. ***Thus, all patients who have been recruited to this study are from Norway, and have been included, operated and evaluated at Oslo University Hospital, only. Thus, it has been performed as a single-center study.***

The project leader, Inger Marie Skogseid, who already prior to this study had extensive experience in international and national collaboration on DBS in movement disorders, will be the daily scientific leader of the project and coordinate the activities of the other participants. At OUS, she will have direct responsibility for the neurological evaluations leading to patient inclusion, the clinical neurological testing during the neurosurgical operations, and the stimulator programming according to the randomization and stimulation parameter protocol. Other qualified movement disorder neurologists at the Department of Neurology, OUH. will assist in this.
To perform the baseline and follow-up neurological scoring and examinations the project has recruited a neurological resident/PhD-student, Nadja Anette Myrvik Kvernmo. The collection of follow-up data for the primary and secondary endpoints will be done by her blindedly with respect to which target is stimulated during the two randomized 3-month periods, and during the following 6 months period. Dr. Kvernmo has since 2015 received 50% salary from a PhD-grant (50 % for 6 years). that was awarded to Inger Marie Skogseid from The South-Eastern regional Health Authorities in December 2014 .
The role of the national/regional collaborators has been to perform the primary diagnostic evaluation of patients at their local hospitals to identify eligible patients. The final evaluation of diagnosis and eligibility of the patients will take place at OUS-Rikshospitalet by the project leader. The collaborators may also, after the randomized study phase is over, make minor adjustments to the magnitude of the stimulation current, without changing the active stimulated contact.

<u>At the project owner institution Oslo University Hospital (OUS):</u>
Department of Neurology, OUS-Rikshospitalet
- <u>Project leader:</u> Consultant neurologist Inger Marie Skogseid. Certified neurologist since 1999, PhD in 2007, now a leading Norwegian movement disorders specialist with more than 10 years specialized experience. Has comprehensive expertise in DBS treatment for all movement disorders

indications (Tremor, Parkinson´s disease, Dystonia) through daily clinical work and research projects focused on DBS treatment since 2003. Helped initiate DBS treatment for dystonia in Norway, through a long-standing collaboration with Professor Jens Volkmann, including participation in the two international, multi-centre sham-stimulation controlled studies of DBS for Generalized/Segmental and Cervical Dystonia, led by him. She is also one of the PIs in an ongoing CRT of STN-DBS in Parkinson´s disease, at OUS-RH. Role in project is outlined above.
- Administrative supervisor: The project has been administered as part of the research portfolio of the Department of Neurology, which until February 2018 was headed by Professor Espen Dietrichs, MD PhD. He has also been the leader of the Movement Disorder Research Group (but has recently resigned from being the formal leader of both of these positions.) His role will be to provide scientific consultation and supervision in the context of the overall research performed by the MDRG. Dietrichs is regarded a leading movement disorders expert in Scandinavia, and has coordinated task forces and research initiatives in the movement disorders field for the past 20 years.
- Other movement disorders doctors/DBS nurse will assist in the programming of stimulators, as this must be done blindedly to the clinical baseline and follow-up evaluations.
- PhD student: As already mentioned, a PhD student has been recruited from amongst qualified neurologist residents. The PhD student contributes 50% effort to the project in parallell with other clinical duties, according to the normal scheme for clinical PhD studies at OUS. The PhD student will work closely together with the Project leader, particularly regarding the collection of baseline clinical tremor scores and other clinical data, and under her direct supervision.

Depts. of Neurosurgery and Neuroradiology, OUS-Rikshospitalet The Section of Functional Neurosurgery has been performing DBS surgery for movement disorders for over 15 years, recently 30-50 new implants per year. The main collaborating neurosurgeon for this project will be/has been consultant Ane Konglund. Neuroradiologist Bård Nedregaard will be responsible for the neuroradiological examinations (MRI including DTI/fiber tracking, helical CT scans), which are performed according to defined protocols. He has extensive theoretical and practical knowledge of MRI, including experience in DTI-fiber tracking. The merging of MRI and CT will be, as already mentioned performed as part of the work-flow at the Wuerzburg Visual DBS Lab team described above, in collaboration with dr. Kvernmo and dr. Skogseid.
Department of Neuropsychiatry: Neuropsychological examinations will be carried out by qualified personell at the department. Neuropsychologist Ana Perez is responsible for the neuropsychological testing, but is assisted by several other psychologists..

Statistical advisor: Are Hugo Pripp, Oslo Centre of Biostatistics and Epidemiology, OUH.

International collaborators:
Professor Jens Volkmann, Head of the Dept of Neurology, University Clinic Wuerzburg, Germany. One of the leading world experts in DBS in movement disorders, for many years principal architect of the DBS research group in Kiel, Germany, which performed some of the most important studies of DBS in tremor, dystonia, and PD in close collaboration with prof. Guenther Deuschl (see ref.).
Martin M. Reich, MD,PhD, University Clinic Wuerzburg, Germany. Specialist in neurology and movement disorders, particular expertise in imaging analysis of DBS electrode localization, with several important paper on this subject during recent years..

National/regional collaborators:
From the Mid-Norwegian Health Region, St Olav University Hospital, Trondheim:
The team specified below agreed to participate in the study, but as mentioned earlier they withdrew within the first half year after inclusion of patients had been initiated at OUH. They concluded at that time that they did not have the personell resources required to participate in the study.

(Professor/Consultant Neurologist, Jan O. Aasly – a leading Norwegian neurologist/movement disorders specialist and researcher. Experienced in DBS treatment in movement disorders. Consultant Neurosurgeon, PhD, Sasha Gulati, and Senior Consultant Neurosurgeon Jan V Jørgensen, both experienced stereotactic/DBS-surgeons.)

National collaborators who have recruited/referred patients to the study:
From the Western Health Region of Norway, Haukeland University Hospital, Bergen:
Professor Ole-Bjørn Tysnes, Head of the Department of Neurology, Bergen University Hospital – a leading Norwegian neurologist/movement disorders specialist and researcher. Experienced in DBS treatment of movement disorders.
Consultant Ken-Freddy Pedersen, Department of Neurology, Stavanger University Hospital. A movement disorders specialist, who was awarded a PhD and is currently a post-doctoral fellow at the Department of Neurology/National Competence Centre of Movement Disorders in Stavanger.

From the South-Eastern Health Region of Norway (> 2 mill. inhabitants):
Consultant/Head of department, Remo Gerdts, Sykehuset Vestfold, Tønsberg
Consultant, PhD, Jeanette Koht, Sykehuset Buskerud, Drammen
Consultant Volker Solyga, Sykehuset Østfold, Fredrikstad
Consultant, PhD, Karen Herlofson, Sykehuset Sørlandet, Arendal/Kristiansand

3. Key perspectives and compliance with strategic documents

3.1. Compliance with strategic documents

The Department of Neurology and Neurosurgery at OUS and the Department of Neurology at St. Olavs Hospital, Trondheim have been assigned by the Norwegian Health Directory the national function of providing DBS for relevant patient groups. The activities included in this study are directly related to specific goals stipulated in research strategy documents at different organizational levels of OUS (**movement disorders**: Research Strategic Plan for Department of Neurosurgery and Neurology; **brain damage/disease**: Research Strategic Plan for Clinic for Surgery and Neuromedicine 2011-2015), at the Norwegian Research Council (**normal and pathological brain function**: NEVRONOR Strategic Plan 2012-2013; **diseases of the nervous system**: KLINMED Program Plan 2011-2015; **brain aging, research-based clinical practice**: Strategic Document 'Flere Aktive og Sunne År'), The Southeast Norway Regional Health Authority (**increased innovation, better clinical service, greater treatment efficacy and cost reduction**; Research Strategy 2008-2012) and the Ministry of Health (**neurological damage and disease**; Strategic Document 'Nevroplan 2015'). The project involves general strategic goals expressed at all of these levels with respect to increase in clinical research competance, increased national and international collaboration, and better health services.

3.2. Relevance and benefit to society

This study will establish better DBS procedures for treating intractable and disabling tremor conditions, providing a significant improvement of this resource-demanding, but very effective treatment. Improved tremor suppression by more exact targeting will increase patient satisfaction, function and integration into society, thus reducing their need for assistance, including subsidized public assistance, such as in nursing homes. The increased benefit from improved integration into the workplace alone represents substantial cost savings for society. Improved tremor suppression will also reduce the need for specialized neurological care at DBS-centres, greatly reducing direct costs and travel costs. These benefits are relevant regionally, nationally and internationally.

3.3. Environmental impact

To our knowledge there are no significant environmental impacts associated with the project.

3.4. Ethical perspectives

Patients (of both genders) will be included only upon written informed consent. Before inclusion of patients was intiated (April 2014), the study was approved by the Regional Committee for Medical Research Ethics (RCMRE) by October 2013 (ref.no 2013/1013), and by the Privacy Ombudsman (Personvernombudet, PO) at OUH- Rikshospitalet (ref. 2013-9948, Tremorstim). Data are stored a secure research server at OUH (K/Sensitivt/Forskning02/2013-9948 Tremorstim).
Study participants are free to withdraw at any point. Patients who do not wish to participate will be offered standard treatment.
Trial registration: At Clinical Trials.gov by May 2017 (ClinicalTrials.gov ID: NCT03156517).

A second written informed consent is obtained for the long-term follow-up study, and together with this consent for video-recording. In connection with this a report of change, with updated protocol was sent to the Regional Committee for Medical Research Ethics (RCMRE) on Oct. 26th 2019.

3.5. Gender issues (Recruitment of women, gender balance and gender perspectives)

Both the Project Leader and one of the Principal Neurosurgeons at OUS are women, as are several other of the consulting and assisting clinicians (overall gender balance of Norwegian participants 9 women, 12 men). The PhD position will be advertized according to institutional policy and strong efforts will be made to recruit qualified women candidates. Several such are on the staff of the Department of Neurology.

4. Dissemination and communication of results

4.1 Dissemination plan

Publication of results in peer-reviewed medical journals. Media, popular science magazines.

4.2 Communication with users

The Project Leader has had close communication with one of the most relevant patient groups (Norwegian Dystonia Association) for many years, and has been a frequent speaker at their annual meetings. Popular lectures and scientific articles will be provided to this and other patient organizations (Norwegian Parkinson Disease Association, Norwegian MS Association) and their magazines. Relevant clinicians (neurologists, neuroradiologists, neurosurgeons, as well as general practitioners) will be informed of project progress through review articles in the Journal of the Norwegian Medical Association (Tidsskrift for den norske lægeforening), presentations in specific clinical fora, and through the Oslo University Hospital website.

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