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Reinier de Graaf

Protocol title: "The effect of the STIL anti-tremor orthosis on reduction of forearm tremor in Essential Tremor patients - a single blind randomized crossover study"

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PROTOCOL SIGNATURE SHEET

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LIST OF ABBREVIATIONS AND RELEVANT DEFINITIONS

ACT	**Active Cancellation of Tremor**
ADL	**Activities of Daily Life**
AE	**Adverse Event**
ANOVA	**Analysis of Variance**
AVG	**General Data Protection Regulation; in Dutch: Algemene Verordening Gegevensbescherming**
CCMO	**Committee on Research Involving Human Subjects; in Dutch: Centrale Commissie Mensgebonden Onderzoek**
CE	**Conformité Européenne**
CIP	**Clinical Investigation Plan**
CRF	**Case Report Form**
DBS	**Deep Brain Surgery**
DOF	**Degree of Freedom**
DSMB	**Data Safety Monitoring Board**
D-QUEST	**Dutch Quebec User Evaluation of Satisfaction with Assistive Technology**
EFE	**Elbow Flexion/Extension**
EPD	**Electronic Medical Record; in Dutch Elekronisch Patiëntendossier**
FFE	**Finger Flexion/Extension**
FPS	**Forearm Pronation/Supination**
FTM	**Fahn-Tolosa-Marin**
PSP	**Progressive Supranuclear Palsy**
GKT	**Gamma Knife Thalamotomy**
GGZ	**Mental Health Care; in Dutch: Geestelijke Gezondheidszorg**
IB	**Investigator's Brochure**
IFU	**Instructions for Use**
IMDD	**Investigational Medical Device Dossier**
IMU	**Intertial Measurement Unit**
METC	**Medical research ethics committee (MREC); in Dutch: medisch-ethische toetsingscommissie (METC)**
MS	**Multiple Sclerose**
MSA	**Multiple System Atrophy**
NCCIH	**National Center for Complementary and Integrative Health**

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PC	**Personal Computer**
QOL	**Quality of Life**
SAE	**Serious Adverse Events**
SIER	**Shoulder Internal/External Rotation**
TETRAS	**The Essential Tremor Rating Assessment Scale**
TMD	**Tuned Mass Dampers**
WFE	**Wrist Flexion/Extension**
WMO	**Medical Research Involving Human Subjects Act; in Dutch: Wet Medisch-wetenschappelijk Onderzoek met Mensen**
WRUD	**Wrist Radial/Ulnar Deviation**

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SUMMARY

Rationale: Essential Tremor (ET) is the *most common movement disorder* affecting approximately 1% of the general population and about 5% of the population over 65 years. ET affects fine motor control of the hands and has functional impact, impairing daily activities such as writing, drinking or dressing. Current treatment options have limited effects on tremor, cause side-effects or are task specific. Therefore, the STIL orthosis is developed; a non-invasive passive anti-tremor orthosis that suppresses the tremor in daily life and is easy to wear. The orthosis needs to be tested on patients to validate the effectiveness of the orthosis. In this study the effect of the orthosis on tremor severity, patient satisfaction and product safety will be assessed.

Objectives:

Primary Objectives:

- To evaluate the effects of the STIL anti-tremor orthosis on tremor severity in ET patients with an invalidating forearm tremor.
- To evaluate the effects of the STIL anti-tremor orthosis on tremor amplitude in ET patients with an invalidating forearm tremor.

Secondary Objectives:

- To assess patient satisfaction with regards to the usability and comfort of the STIL anti-tremor orthosis.
- To assess the possible adverse effects of the STIL anti-tremor orthosis.

Study design: Single-blind randomized crossover study.

Study population: ET patients over 18 years old with an invalidating forearm tremor.

Intervention: Tremor data will be collected in three conditions: without orthosis (baseline), with orthosis (intervention) and with a sham-device. The order of the modes will be randomly assigned. The investigational device uses the principle of applying external joint damping as its working principle. The sham-device looks and weights the same as the investigational device, however it has no damping elements to suppress the tremor.

Main study parameters/endpoints: The primary study parameter is tremor severity measured using the TETRAS scale and the co-primary study parameter is tremor amplitude.

A secondary parameter is patient satisfaction using D-QUEST, another secondary parameter is product safety using NCCIH's Adverse Events Report Form.

Nature and extent of the burden and risks associated with participation, benefit and group relatedness: The burden associated with participation is low. Participation includes filling out a questionnaire and a hospital visit of maximum one hour to check for eligibility. Once included, the assessment with orthosis in the hospital will take another 30 minutes to one hour. No therapeutic effects are expected; the orthosis is expected to suppress the tremor when being worn. This effect is not expected to last after detaching the orthosis. Based on the exhaustive risk analysis, only minimal risks can be associated with this study. Patients are not at high risk; the two devices only interact with intact skin for a maximum of 30 minutes each (one hours in total) and precautionary measures are taken in case the orthosis does not function as expected.

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1. INTRODUCTION AND RATIONALE

Essential Tremor (ET) is the *most common movement disorder* affecting approximately 1% of the general population and about 5% of the population over 65 years[19]. ET is characterized by a (mostly symmetrical) tremor of the upper limbs, sometimes involving the head and more rarely the voice, trunk and legs [28,2,10]. The tremor is both postural and kinetic, indicating that the tremor occurs during voluntary movement and when the limb is positioned against gravity[28]. ET affects fine motor control of the hands and has *functional impact*, impairing daily activities such a writing, drinking, or dressing [2,32]. These impairments may also have *social impact*; patients are often ashamed of their inability to participate in social of working activities, leading to avoidance of social events[33].

There are several ways to treat ET. *Medication* (propranolol or primidone) is usually tried first to control tremor, but many patients experience side effects and in most cases the tremor will not completely disappear [2,7,15]. Stereotactic surgery is another widely used treatment, of which *deep brain stimulation* (DBS) used to be the golden standard [2,32,7]. DBS can reduce the tremor, but is not applicable for every patient [16,29]. Moreover, side effects are reported, including paresthesia, dystonia, gait, balance disturbance and ataxia [2,32,7,22,17]. Besides, hemorrhage and infection can occur due to craniotomy [28]. Another stereotactic surgery is *Gamma Knife Thalamotomy* (GKT) [14] which creates a lesion in the brain by delivering external radiation. It aims to reduce the tremor, by destroying the cells that are involved in the tremor origination [32,7,14]. However, like DBS, this surgery is not suitable for every patient and since it is invasive, not many patients are willing to undergo such a treatment.

The treatments mentioned above target the cause of the disease, while another approach is to suppress the symptoms. Nowadays, tremor suppression techniques are found in *orthotics*. These are devices which mechanically attenuate or dissipate forearm or wrist tremors that have made their upswing in recent years [23,30], but do still not provide a practical solution for everyday use. The problem is that often active orthoses rely on actuators coupled to a signal transmission system, resulting in a heavy and unwieldy device [20]. Other alternative solutions are designed for specific tasks, such as eating with a spoon (e.g., Liftware Spoon[23]).

Tremor occurs in all parts of the upper extremity, most present in the:

- shoulder internal/external rotation (SIER)
- elbow flexion/extension (EFE)
- forearm pronation/supination (FPS)
- wrist flexion/extension (WFE)
- wrist radial/ulnar deviation (WRUD)
- finger flexion/extension (FFE)

The currently available passive devices often only tackle suppression in a single degree of freedom (DOF). Strong evidence is found that suppressing a single DOF will not provide relief for tremor patients [25].

This indicates that current treatment options have limitations. Therefore, the STIL anti-tremor orthosis is developed; a non-invasive, passive, anti-tremor orthosis that suppresses tremor in multiple relevant DOFs to provide relief in daily life and is easy to wear. A prototype of the orthosis is depicted in Figure 1.

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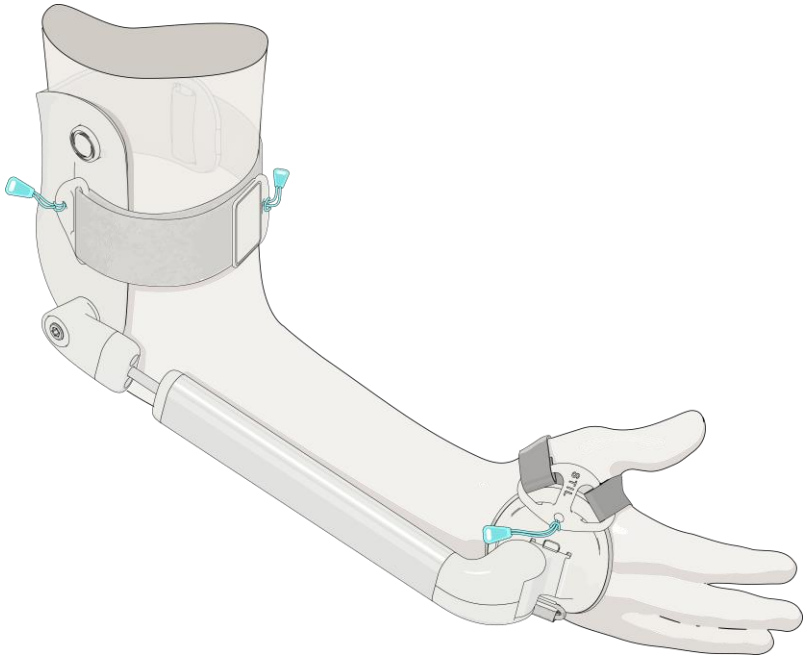

***Figure 1**: Rendered image of the STIL anti-tremor orthosis. The medical device suppresses tremor in the forearm by applying additional damping to the wrist flexion/extension (WFE) and the forearm pronation/supination (FPS).*

The working mechanism of the orthosis makes use of two passive dampers which exert a damping torque to the wrist and forearm joints. The dampers are designed to restrain high angular velocity more than slower angular velocity. As such, wrist flexion/extension (WFE) and forearm pronation/supination (FPS) tremor are suppressed by the dampers. Wrist radial/ulnar deviation (WRUD) is suppressed since the orthosis restricts this motion in general.
In this manner, high frequency involuntary movement in the forearm, such as tremor, is suppressed but voluntary motion is still allowed. By suppressing the tremor, activities of daily life (ADL) will improve, as well as participation in social activities.

Market research is performed to take patients' interests and needs into consideration. The results showed a high willingness to adopt to a wearable device for tremor suppression, regardless of the attention that the device possibly attracts. This portrays the dissatisfaction of the current treatment and situation, and the need for a more suitable alternative.
The anti-tremor mechanism has not yet been evaluated in a clinical environment. Also, patient satisfaction with regards to STIL's anti-tremor orthosis is another factor that needs to be evaluated. User involvement is important in this stage of product design and development. In this way patients' feedback will be taken into account before the final product will get on the market. Altogether, this stresses the need for a study in which the orthosis is evaluated on patients, which we aim to do in the present study.

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2. OBJECTIVES

2.1 Primary Objectives

The primary objective of this clinical investigation is to assess the performance of the orthosis, divided over two co-primary objectives:

1. To evaluate the effect of the STIL anti-tremor orthosis on tremor *severity* reduction in Essential Tremor patients with an invalidating forearm tremor.
2. To evaluate the effect of the STIL anti-tremor orthosis on tremor *amplitude* reduction in Essential Tremor patients with an invalidating forearm tremor.

The co-primary objectives have two endpoints. The endpoint of the first primary objective is the assessment of the TETRAS scale by a trained neurologist(s). The expectation is that the orthosis will reduce tremor *severity* by one measure on the TETRAS scale (e.g. from severe to moderate). The endpoint of the second primary objective is achieved by measuring arm motion with an IMU sensor. The expectation is that the orthosis will reduce tremor *amplitude* by more than 60%.

Together, the primary endpoints give a comprehensive evaluation of the performance of the device.

2.2 Secondary Objectives

Apart from performance objectives, the intervention with the orthosis shall also be assessed on usability and comfort and safety with two primary objectives:

1. To assess patient satisfaction with regards to the usability and comfort of the STIL anti-tremor orthosis.
2. To assess possible adverse effects of the STIL anti-tremor orthosis.

The endpoint of the first secondary objective is the Dutch version of the Quebec user evaluation of satisfaction with assistive technology (D-QUEST) questionnaire, providing a subjective outcome of the usability and comfort of the orthosis from the patient's perspective. The endpoint of the second secondary objective is a listing of (possible) adverse effects, observed either by the investigator and noted down in a (S)AE report form, or as mentioned by the patient in de D-QUEST questionnaire.
Together, the secondary endpoints provide an assessment on safety, comfort and usability of the device.

The health-related quality of life (QoL) will also be evaluated, as this could influence satisfaction from the secondary objective.

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3. STUDY DESIGN

This single-blind randomized crossover study will take place at the neurology department of the Reinier de Graaf hospital in Delft.

Tremor severity and amplitude will be measured in three conditions: without orthosis (*baseline*), with a sham-device *(sham)*, and with the anti-tremor orthosis (*intervention*). The order of the devices will be randomly assigned by a software specifically designed to aid the investigation. The sham device looks and weighs the same as the anti-tremor orthosis, however it does not contain the working mechanisms used to suppress the tremor. The patient does not know the order of the devices. In this way, single-blinding is guaranteed.

Health-related QoL will be assessed prior to the start of testing with the orthosis, as it could possibly intervene with patient satisfaction. Tremor severity and satisfaction with the devices will be assessed after using a device.

A schematic overview of the study design is depicted in Figure 2. Patient inclusion will be evaluated based on the criteria described in Section 4. Patient inclusion is executed in two steps: first by evaluation of a questionnaire which the patients fill in remotely, and second by a physical evaluation during an appointment in the hospital.

During this appointment in the hospital, patients are asked to perform 7 movement tasks. The movement during tasks will be registered with motion sensors and video-recorded to allow evaluation afterwards.

When the principal investigator is confident that a patient is eligible and he/she is willing to participate, the next part of the appointment – i.e. testing the orthosis and the sham-device – will follow directly. The earlier obtained results of the 7 tasks will be used as the baseline condition.

If the principal investigator is unsure if the patient is eligible, the patients is sent home after max. 1 hour. Additional video analysis will determine if the patient is eligible to continue with testing the orthosis. If so, the patient is invited for a second appointment of max. 2 hours, where again is started with 7 movement tasks without orthosis (baseline), followed by testing the orthosis and the sham device in random order.

This protocol allows for minimal impact on the patients, since only a single visit of two hours to the hospital could be sufficient. The study has started in March 2022 and should be finished by December 2022.

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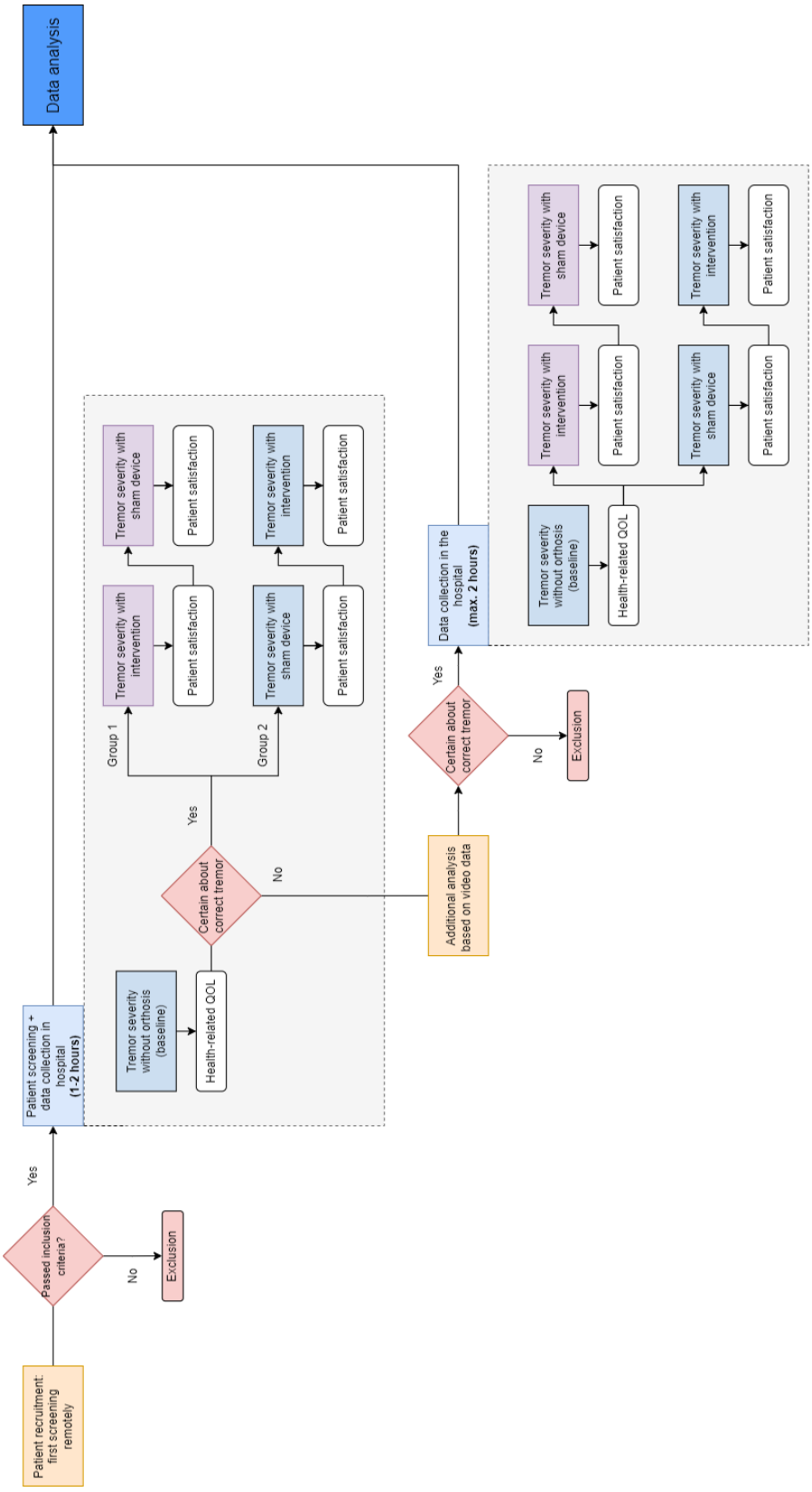

***Figure** 2: Flowchart of the study design*

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4. STUDY POPULATION

4.1 Population

Tremor is the most common movement disorder and is defined as 'an involuntary rhythmic oscillation of a body part, mediated by alternating contractions of reciprocally acting [28]. Tremors can be classified in a number of ways, based on the frequency, amplitude and affected body part. Besides, there are different neurological disorder that can cause the tremor, for example Essential Tremor, Parkinson's Disease, dystonia and Multiple Sclerosis [28]. Finally, distinction can be made in the type of tremor: resting tremor (the tremor occurs when the limb is in rest) and action tremor (the tremor occurs during voluntary movement or when the limb is positioned against gravity) [28].
Patients that will be included in this study must be over 18 years old and must have an invalidating forearm tremor. This implies that they have difficulties in performing daily activities as scored with the ADL self-assessment questionnaire by Bain and Findley [1]. In the present study, invalidating tremor is defined as having a minimum subscore of 30 across all upper limb items and an ADL score of at least 3 in at least one upper limb item. In case of doubt regarding in- or exclusion criteria, the judgement of the principal investigator prevails over the self-assessed judgement of the patient.
The typical population in which this tremor is observed are patients diagnosed with ET, as described in the introduction. However, diagnostic criteria are not strict and there is no golden standard for this diagnosis[2,13]. Therefore, misdiagnosis can occur, since the same invalidating action tremor is (although less frequently) observed in other neurological disorders, such as Parkinson's Disease, dystonia and Multiple Sclerosis.

4.2 Inclusion criteria

Based on comparable studies [12,3], the following inclusion criteria are defined for participants:

- Participant is at least 18 years of age.
- Willing to sign the informed consent.
- Diagnosed with Essential Tremor.
- Significant disability due to forearm tremor. A minimum subscore of 30 across all upper limb items, scored for the most affected arm/hand with the Bain and Findley ADL scale [1].
- A tremor severity subscore of 13 or higher in the arm/hand as measured by 7 rated TETRAS[9] tasks. The posture and ADL tasks are assessed using the scale used to assess the upper limb tremor.
- A predominant FPS and/or WFE tremor - with minor influence of SIER, EFE and FFE tremor - according to the principal investigator's judgement. When no clear judgement can be formed, assessment of DOFs using TETRAS' upper limb tremor scale can be performed using the method in Appendix I.
  Note: a predominant FPS and/or WFE tremor with the absence of a SIER, EFE and FFE is defined as: a rating below 1,5 in the SIER in a maximum of two rated TETRAS tasks AND below 2 in the EFE and FFE in a maximum of two rated TETRAS tasks

The amplitude of the postures and ADL tasks is rated peak-to-peak using TETRAS' upper limb tremor scale. More thorough instructions on how the tremor DOFs are assessed are included in Appendix I.

4.3 Exclusion criteria

- Dominant shoulder internal/external rotation tremor.
- Dominant elbow flexion/extension tremor.
- Excessive alcohol consumption, as defined in the GGZ guidelines on alcohol use [21].

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- Previous or planned Deep Brain Stimulation (DBS) at time of study enrollment that interferes with testing.
- Previous or planned thalamotomy procedure, including stereotactic thalamotomy, gamma knife radio surgical thalamotomy, and focused ultrasound for the treatment of tremor at time of study enrollment that interferes with testing.
- Change in medications related to tremor disorder in the 30 days prior to study enrollment.
- A hand circumference smaller than 170 mm, or larger than 250 mm.
- An upper arm circumference smaller than 180 mm, or larger than 350 mm.
- Swollen, infected, inflamed areas, or skin eruptions, open wounds, or cancerous lesions of skin on the forearm or hand that would wear the orthosis during the clinical investigation.
- Peripheral neuropathy affecting the tested upper extremity (e.g. Carpal tunnel syndrome)
- The suspicion or confirmation that head tremor may cause impairment in performing ADL tasks.
- Diagnosed Parkinson's disease, this includes presence of parkinsonian features.
- Diagnosed functional tremor.
- Diagnosed physiologic tremor.
- Diagnosed cerebellar tremor.
- Diagnosed Multiple Sclerosis (MS).
- Diagnosed ataxia.
- Patients with an amputation of one or both upper extremities.
- Subjects with a restricted movement or restricted muscle function in the arm and or hand (e.g. contractures).
- Botulinum toxin injection for hand tremor within 6 months prior to study enrollment.
- Alcohol or caffeine consumption within 10 hours of study enrollment.
- Heavy physical training within 10 hours of study enrollment.
- Subjects unable to communicate with the investigator and staff due to:
    - Not mastering the Dutch language.
    - Blindness.
    - Deafness.
- Subjects with illiteracy.
- Pregnancy or anticipated pregnancy at time of study enrollment.
- Any health condition that in the neurologist's opinion should preclude participation in this study.

4.4 Sample size calculation

The first primary outcome measure, the TETRAS score, is normally distributed [30]. The seven performed tasks are rated on a 0-4 scale of which three with halve points. When the scores are summed, the total outcome has a resolution of 3*9 + 4*5 = 47 steps, and can be seen as a continues outcome measure.
The second primary outcome measure, IMU measurements, is continuous and has a logarithmic relationship with respect to the TETRAS scale and is therefore lognormally distributed[8]. After applying a logarithmic transformation, the IMU data will also be normally distributed [11].

Given the above characteristics of the outcome measures (see Section 2) and the crossover study design (see Section 3), the sample size has been calculated with G*power using a two-tailed matched pair t-test.

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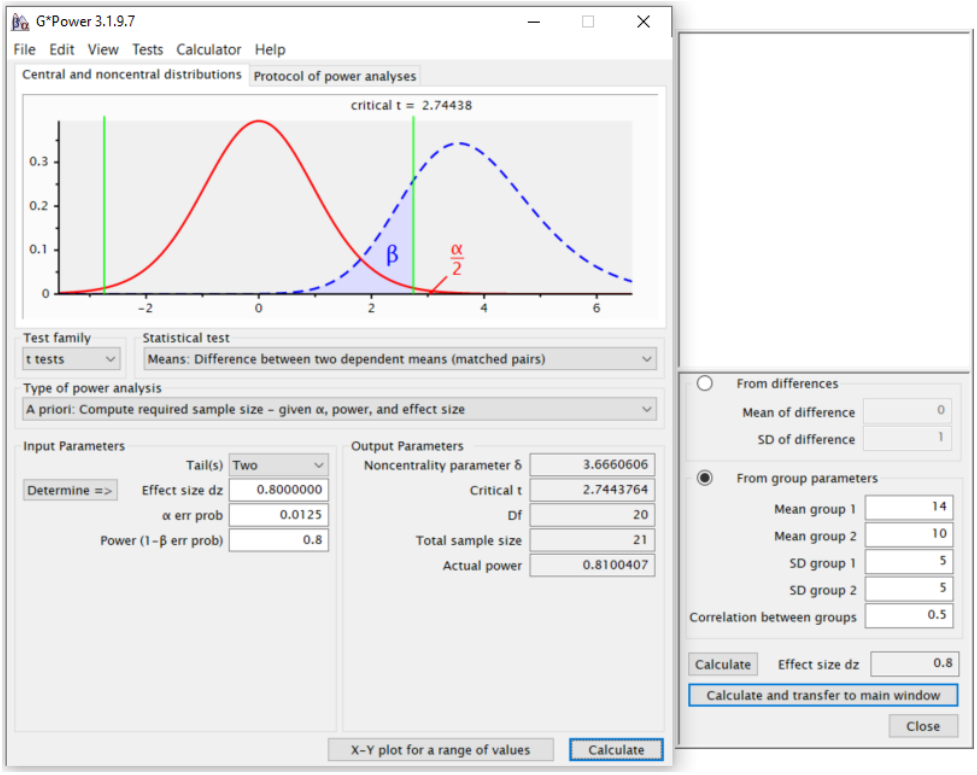

*Figure 3: G*Power calculation*

Four studies, in which the effect of an active hand device on tremor amplitude is investigated, are used to estimate the effect size. Two of these studies did not use mechanical suppression, but reduced the tremor by means of nerve or muscle stimulation. More information about these studies can be found in Section 6.2 and 6.3.

- Steadi-One; a mechanical device which uses of fluids for reducing amplitude of motions [20]. Results show those patients who improved by kinematic analysis had a 0.81-point score clinical improvement. There was a 0.57-point improvement in dynamic tasks based on the Fahn-Tolosa-Marin clinical rating scale (FTM) [31].
- The study of Lin et al. (2018) evaluated the CALA wrist device that used nerve stimulation to reduce hand tremor. This study showed a tremor amplitude reduction of 60% ± 8.4% (n = 23) which was significantly greater in the treatment than in the sham group [18].
- The Liftware Spoon, a handheld assistive device which also makes use of active cancellation of tremor, reduced the tremor amplitude with 73% ± 13% (n = 11) [24].
- The out-of-phase wrist device that uses electrical stimulation of antagonistic muscle of Maneski et al (2011) showed a significant reduction in tremor amplitude of 67% ± 13% (n = 7) [26].

Given the fact that the effects showed in other anti-tremor device studies were large, and the patients only benefit from a device that has a large effect on their tremor, the effect size d 0.8 was chosen [27].
An example calculation where the orthosis reduces 4 points (out of 28 total) on the TETRAS scale, assuming a standard deviation of 5 for both groups, generates this effect size of 0.8 (see Figure 3).

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In total, 4 conditions will be compared with 2 different outcome measures; baseline vs. intervention (TETRAS), sham vs. intervention (TETRAS), baseline vs. intervention (IMU data) and sham vs. intervention (IMU data).
Taking into account a worst-case scenario of type 1 errors accumulation over the 4 testing conditions, a Bonferroni correction of alpha = 0.05/4 = 0.0125 is used.
The power value of 0.8 has been used, since this value is common practice in medical literature.

Using the above-mentioned parameters, it can be concluded that a minimum of 21 patients is needed. In order to compensate for possible drop-outs (10%), 25 patients will be included for this clinical investigation.

If the data is not normally distributed (after log compensation), unlike described in literature, the statistical analyses can also be performed by means of 4 Wilcoxon matched pair tests. This has no consequences for the sample size, since the sample size analysis in such case will result in 22 patients.

5. TREATMENT OF SUBJECTS

5.1 Investigational product/treatment

The device that will be tested in this study is the STIL anti-tremor orthosis. This non-invasive passive device uses the principle of applying external joint damping as its working principle. Two types of dampers are used to restrict high frequency involuntary motion, leaving low impact on voluntary motion, to passively suppress the forearm tremor. This will support ET patients in their daily and social activities.

A sham device is used to investigate and eliminate the influence of the weight of the STIL orthosis on tremor suppression and to validate the working principle of the dampers. The sham device used has no damping elements, but has a similar look and weight (see *IMDD chapter 1.1.i*).

5.2 Use of co-intervention

As written in the inclusion and exclusion criteria, patients may not have changed their medication in the 30 days prior to study entry. An implanted electrical deep brain stimulator is not allowed. Besides, patients may not consume caffeine or alcohol in the 10 hours prior to study enrolment. Caffeine is known to intensify tremor, while alcohol may suppress the tremor.

5.3 Escape medication

Does not apply to this study.

6. INVESTIGATIONAL PRODUCT

6.1 Name and description of investigational product

The STIL anti-tremor orthosis consists of an elbow piece and a hand piece, connected by a rigid extension element, via a total of 3 joints. The wrist and forearm joints are equipped with passive dampers which exert an additional damping to the respective joint. In this manner, high frequency involuntary movement, such as tremor, is suppressed but voluntary movement is still allowed. In this study, the beta-prototype (pre-market release version) of the orthosis will be

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tested (Figure 1). The device is completely passive, and thus does not require software or electronics for its operation.

6.2 Summary of findings from non-clinical studies

- The study of Belda-Louis et al. (2003) identified tremor joint torques on a study of 18 patients, with different demographics and sexes. The dampers used to suppress the tremor are selected based on their findings regarding joint torque per DOF and per tremor type. The joint torque values in kinetic tremors are taken as reference point, as these involve tasks in which ET patients are most hindered. For suppression in the WFE tremor, a damper with a same damping torque was used. For the FPS tremor, a lower damping torque is used. Based on testing with healthy subject, it was found that a higher torque would obstruct voluntary motion too much. This provides the proof that tremor could theoretically be counteracted with the investigational device.
- A representative version of the investigational device has been tested in an internal feasibility study to test the safety, comfort and hygiene of the orthosis. Six healthy volunteers wore the orthosis for 8 hours, spread over 1-2 days. No severe adverse events were reported. More information on this is found in *IMDD Appendix VIII*.

6.3 Summary of findings from clinical studies

To date, no clinical studies have been performed with the STIL orthosis. However, clinical studies investigating the effects of both active and passive devices on tremor amplitude and severity, have been conducted in the past.

- The study of Lin et al. (2018) evaluated the CALA wrist device. This device uses nerve stimulation as a non-invasive therapy to aid in the symptomatic relief of hand tremor. Subjects were randomized to treatment or sham groups. A significant tremor reduction of 60% ± 8.4% (p = 0.02) was found in the treatment group compared to the sham group. Blinded rater scores (TETRAS) significantly improved following stimulation (1.77 ± 0.21) compared with pre-stimulation (2.77 ± 0.22) [18].
- The Liftware Spoon; a non-invasive handheld device using Active Cancellation of Tremor (ACT) technology to stabilize an eating utensil. The ACT system senses tremor direction and moves the spoon in the opposite direction to stabilize it. In this double-blinded study, patients performed certain tasks with and without stimulation of the device. Results showed a reduction of tremor amplitude of 73% ± 13% with stimulation of the device. Rater scores (Fahn-Tolosa-Marin rating scale) improved significantly during three tasks with stimulation (holding: 1.00 ± 0.76 vs. 0.27 ± 0.70, eating: 1.47 ± 1.06 vs. 0.13 ± 0.64 and transferring: 1.33 ± 0.82 vs. 0.27 ± 0.59)[24].
- Steadi-One; a mechanical device that integrates a tuned mass damper contains a non-Newtonian fluid to suppress tremors. When vibration energy is transferred to the added mass, this fluid become viscous, reducing its amplitude of motions [20]. Results show those patients who improved by kinematic analysis had a 0.81-point score clinical improvement. There was a 0.57-point improvement in dynamic tasks based on the Fahn-Tolosa-Marin clinical rating scale (FTM) [31].

6.4 Summary of known and potential risks and benefits

Patients that will be included are not vulnerable or at high risk of getting hurt, the devices only interact with intact skin for a maximum of one hour and precautionary measures are taken as

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described in Section 12. Therefore, no severe adverse events are expected in this study. Several precautionary measures are taken to mitigate possible negative effects in the unlikely event that the device does not function as expected.
Patients will not directly benefit from participating in the sense that it may cure their disorder. The tremor is expected to be suppressed when the orthosis is properly fitted, but this effect will not last after detaching the orthosis. Patients' satisfaction with the device will be assessed, which is a valuable input for the further development of the orthosis. Their feedback, as assessed with the satisfaction questionnaire, will help to optimize the design of the orthosis.
A more thorough risk and benefit analysis is described in *IMDD chapter 5.*

6.5 Description and justification of route of administration and dosage

A custom verified CRF software package, which also includes an API to acquire the motion and video data, will determine the randomization process of the study procedure.

1. Place the orthosis on the table parallel to the arm.
2. Slide the elbow into the elbow cuff, the humeroradial joint of the elbow must be aligned with the joint on the orthosis, which connects the sliding parts with the cuff.
3. Fasten the elbow cuff by hooking the fastener in the designated slot. Adjusts the tightness of the strap to where the cuff fits secure yet comfortable.
4. Slide the handpiece, using the extension element, to an extent where the handpiece is level with the center of the palm.
5. Place the hand with the dorsal side in the hand piece.
6. Put the thumb between the two straps and fastens the hand piece by hooking the fastener in the designated slot. Fasten the strap to where the cuff fits secure yet comfortable.

More detailed instructions on how to put on the orthosis can be found in Appendix II of the IMDD.

6.6 Dosages, dosage modifications and method of administration

See section 6.5.

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7. METHODS

7.1 Study parameters

7.1.1 Main study parameter

- Quantification of tremor severity will be based on the TETRAS scale, from which 7 tasks (postural out-stretched arms, postural wingbeat, finger-to-nose, eating, drinking, pouring, Archimedes spiral) are selected that accurately represent the obstruction that ET patients experience in daily life. A TETRAS score is rated on the baseline, sham and intervention conditions. Combining the 7 tasks from the TETRAS scale, a maximum scoring of 28 points can be achieved per condition.
- The co-primary quantification of tremor amplitude will be based on movement data from an Inertial Measurement Unit (IMU). Again, the same 7 tasks (postural out-stretched arms, postural wingbeat, finger-to-nose, eating, drinking, pouring, Archimedes spiral) are used to compare baseline, sham and intervention conditions. A measure for overall tremor amplitude is calculated per test subject, for every selected TETRAS task.

7.1.2 Secondary study parameters

- The secondary study parameter, patient's satisfaction, will be scored to test patient satisfaction with regards to comfort and usability of the orthosis with the Dutch Quebec User Evaluation of Satisfaction with Assistive Technology (D-QUEST) [6,5]. This questionnaire consists of 8 questions about the device itself and 5 questions about the service of the manufacturer. Only questions about the device itself will be questioned. Satisfaction is measured on a 1-5 scale, ranging from 'completely not satisfied' to 'very satisfied'. Additional questions, provided by STIL, will be asked to examine comfort, usability, willingness to wear and possible adverse-effects more detailed.
- The other secondary study parameter, product safety, will be collected by the principal investigator using the Dutch version of NCCIH's Adverse Events Report Form. This form is used to report the severity, relationship to the study, taken action, outcome of the AE and whether it was expected or not.

7.1.3 Other parameter

- Another parameter, health-related quality of life, will be assessed using EQ-5D-5L. This questionnaire combines a descriptive system and a visual analogue scale to used health-related quality of life, which could possibly intervene with the patient's satisfaction.

7.2 Randomisation, blinding and treatment allocation

Tremor severity will be assessed in three situations: without wearing the orthosis (baseline), with the sham orthosis (sham) and with the anti-tremor orthosis (intervention). An algorithm within the CRF software, which includes the API that is used to acquire the motion data, will randomly determine the order of the sham device and intervention. Only the investigator can see which device is selected, thereby blinding the patient. The investigator will obtain the selected device,

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using color-coded tabs, and attach it to the patient's arm/hand. Both the devices will have a comparable look and weight (see *IMDD chapter 1.1.i*).
Tremor amplitude can be affected by adding passive weight. By evaluating the sham device, the effects of the weight of the orthosis on tremor suppression will be taken into account. It is also used to evaluate the possible placebo-effect on tremor reduction. Because the investigator knows which variant is being tested, the data will be placed with the corresponding variant in the digital CRF. The patient will be seated in such way that it is not possible for him/her to view the CRF. This eliminates the need to decode the collected data.

7.3 Study procedures

7.3.1 Selection procedure

1. Patient screening
Patient screening will primarily rely on screening by the principal investigator or from other neurologists in the Reinier de Graaf hospital. The treating physician can select his/her patients which are deemed suitable, to inform about them about the study. To avoid overlooking suitable candidates and in case the number of manual screened patients are not sufficient, CTcue – a software extension within the hospital's EPD used for searching patients – is used to perform an additional screening of the patients in the database, based on several criteria from the inclusion and exclusion protocol. Here, for instance, patients can be excluded who have the wrong tremor diagnoses.
Patients in CTcue will be pseudonymized, and will receive a unique identifier number. Only the attending neurologist will have access to the translation key. It is assumed that most of the patients fall within the scope of the principal investigator, because of his specialism on movement disorders within the Reinier de Graaf hospital.
In case the screened patients are attended by a different neurologist, permission will be obtained to get access to the file.
Besides screening via the Reinier de Graaf hospital, a brochure will be used to recruit additional patients suitable for the study. This brochure will be shared via appropriate (social) media channels, or to affiliated neurologists from other Dutch hospitals. In this way, ET patients outside of the Reinier de Graaf hospital can themselves, independent from their physician, contact the investigator(s) directly for more information. To filter out requests, the investigator will ask a few elementary questions from the inclusion criteria (e.g.: "Are you diagnosed with ET") to validate if patients should receive a formal patient information form.

2. *Pre-selection of patients*
Eligible patients will receive patient information and informed consent via mail. Furthermore, Bain and Findley's ADL questionnaire will be added in the application form, together with additional questions to check for the other inclusion and exclusion criteria. Patients will also be provided with a reply envelope in which they can return the questionnaires free of charge, if they want to participate. Additionally, if a patient is willing to participate, he/she fills out the application form and returns it by mail within two weeks. These patients will be checked for eligibility by the investigator. Patients who meet all the preliminary inclusion criteria will be contacted by phone to schedule an appointment for

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the next step in the inclusion process. In case the patient has not responded in two weeks, he/she will receive a reminder letter via mail. Patients who returned the application form, but do not meet the inclusion criteria, will be informed via phone that they are not eligible for participation. If patients have additional questions, they can always contact the principal investigator or independent experts.

3. Inclusion of patients

The next step requires a visit to the hospital; this appointment will last for a maximum of one hour and takes place at the neurology department of the Reinier de Graaf hospital in Delft. Time will be taken to make the patient feel at ease, to make sure that the patient is not nervous or stressed which may increase tremor severity. The patient is allowed to drink something at this moment (caffeine and alcohol free). This is also when the procedure will be explained and allows a moment for the patient to ask questions. During this appointment, patients will be asked to perform the 7 selected TETRAS tasks (see Section 7.3.4), which will be videorecorded. Two synchronized webcams will record the tasks, which will be done for both the left and the right side. The IMU sensors will be attached on the wrist and hand to record the motion data (see Section 7.3.3). If the patient seems suitable for testing the orthosis, the IMU and video recordings will be used to indicate the tremor severity of the patient without orthosis (baseline).

The hand and upper arm circumference will also be measured by the investigator, these can later be used to select the correct size of the orthosis (S, M, L). If, after this step, the judgement can be drawn that the patient is suitable for the study, meaning that all inclusion- and exclusion criteria (see Section 4.2 and 4.3) are fulfilled, the assessment with the orthoses will directly follow. In preparation for this intervention, it will be determined which arm will be tested, including which size. If only one side turns out to be eligible (left or right), then that side shall be used to test the intervention. If both sides are eligible, the dominant arm as defined by the patient shall be used.

After the TETRAS tasks in baseline condition, the video recordings will be assessed by the principal investigator, where tremor severity and dominant tremor DoF is evaluated.

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7.3.2 Introduction to the intervention

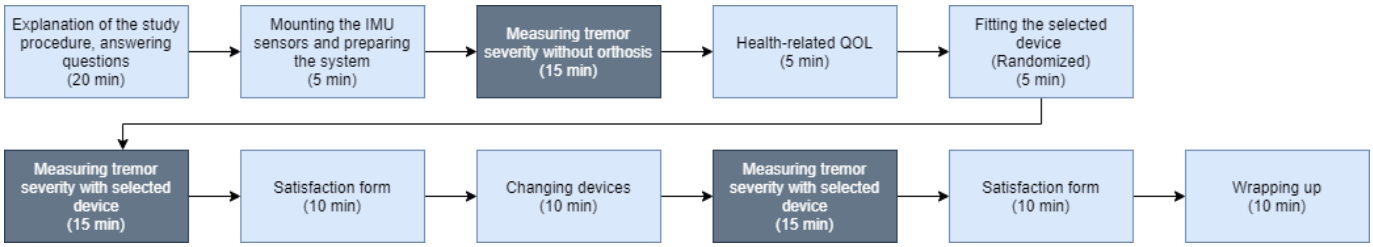

Figure 4. *Global time planning of the testing with the orthosis.*

The assessment will last for maximum two hours and takes place at the neurology department of the Reinier de Graaf hospital in Delft. A global time planning can be found in Figure 4. When a patient comes in, the procedure of the study will be explained to prepare the patient for what is coming. Time will be taken to make the patient at ease, to make sure that the patient is not nervous or stressed which may increase tremor severity. The patient is allowed to drink something at this moment (caffeine and alcohol free).

7.3.3 Sensor placement and amplitude assessment

The investigator attaches the IMU sensors (Xsens MTw Awinda), which record motion data, to the subjects' wrist and hand. The first sensor is attached to the middle and ring finger with a Velcro strap. The second sensor is attached ventral side of the wrist, also with a Velcro strap. See Figure 5.

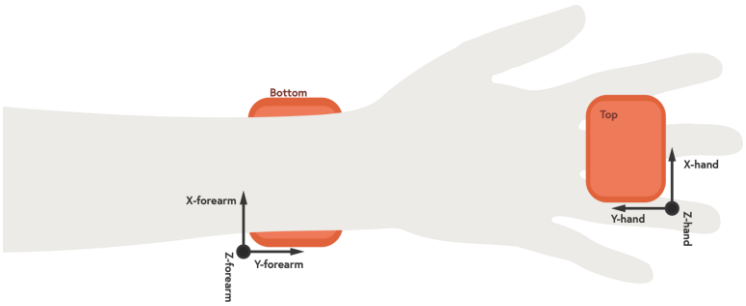

Figure 5: *Placement of Xsens motion sensors on the ventral side of the wrist and the middle and ring finger*

Hereafter, the arm motion, and also the tremor amplitude, can be recorded when the investigators enable the sensors in the software package, which includes APIs for connecting with their hardware. This motion data will only be collected while performing different movements and postures as explained below.

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7.3.4 Tremor severity assessment using TETRAS

The principal investigator will quantify the tremor severity using the TETRAS scale. The principal investigator is adequately trained to carry out this assessment. To minimize investigator bias, a second opinion from an independent neurologist will be consulted. These movements and postures are derived from the TETRAS scale [9] and patient will be asked to perform them for 30 seconds:

- **Eating with a spoon:** Using a spoon to bring peas from a bowl on the table to the mouth. This is an adaptation from the TETRAS scale, as it usually does not specify which solids or liquids must be used to assess eating with a spoon.
- **Drinking from a cup:** Bringing a cup (8 cm tall, filled with water to 1 cm from top) from the table to the mouth to drink water.
- **Pouring:** Pouring a water filled plastic cup (8 cm tall, filled with water to 1 cm from top) into another cup (8 cm tall) that is unsupported on the table.
- **Forward outstretched posture:** Subjects will bring their arms forward, slightly lateral to midline and parallel to the ground. The wrists should also be straight and the fingers abducted so that they do not touch each other (Figure 6).
- **Lateral "wing beating" posture:** Subjects will abduct their arms parallel to the ground and flex the elbows so that the two hands do not quite touch each other and are at the level of the nose. The fingers are abducted so that they do not touch each other (Figure 6).

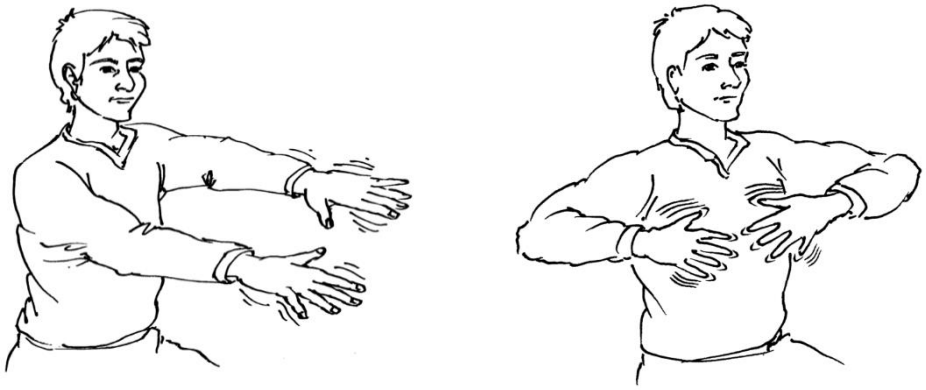

Figure 6. *Forward outstretched posture* *Lateral wing beating posture*

- **Finger-nose-test:** Subjects extend only their index finger. They then touch the examiners finger located to the full extent of their reach, which is located at the same height (parallel to the ground) and slightly lateral to the midline. Subject then touch their own nose (or chin if the tremor is severe) and repeat this back and forth.
- **Archimedes spiral**: Subjects are asked to copy an Archimedes spiral using a ballpoint pen that approximately fills an A6 sheet of paper (Figure 7). The lines of the spiral should be approximately 1.3 cm apart. The pen should be held in such way that no part of the limb touches the table.

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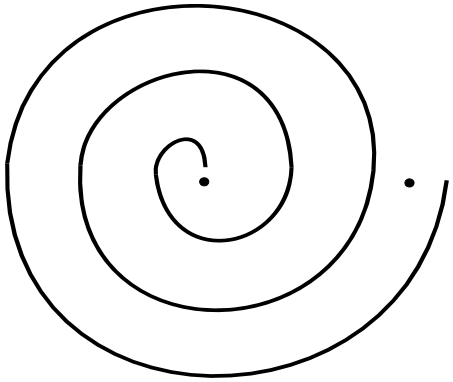

***Figure 7**. Archimedes spiral. The patient will be asked to draw a spiral between the lines, connecting the two dots.*

While performing the tasks for 30 seconds each, motion data is collected simultaneously with the video footage. These are all recorded in the digital CRF and stored on a secure network drive.

7.3.5 Cross-over test procedure

The study is designed to be a cross-over study, where baseline is compared to the intervention, and sham is also compared to the intervention.
The assessment procedure in Sections 7.3.3 and 7.3.4 will therefore be repeated 3 times, like is depicted in Figure 4.
The first condition is the baseline condition without orthosis. In the second and third condition, the sham device and anti-tremor orthosis will be tested, in randomized order. The CRF software determines the randomization.
The investigator will fasten the orthosis as explained in Section 6.5. The IMU sensors can stay attached at the same places as in the baseline condition.

7.3.6 Satisfaction assessment

Once the data for either the sham or intervention has been collected, the investigator removes the device from the patient's arm. The patient is then asked to fill out the satisfaction questionnaire (D-QUEST). Satisfaction is collected after both the sham and the investigational device. The investigator can help if the patient has writing difficulties. Before the patient leaves, all questionnaires will be checked thoroughly on completeness to prevent missing data.

7.3.7 Reporting Adverse Events

During the entire visit, the principal investigator will report every observed adverse event using the Adverse Event (AE) Report Form. This form will specify the severity, relation to the study intervention, the taken action, the outcome, the expectancy and whether the event was a SAE of the AE. If SAEs have been observed, they must be reported by the sponsor

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though the web portal of *ToetsingOnline,* more information can be found in Section 8*.*

7.3.8 Health-related Quality of Life

After the first condition (baseline) health-related QoL will be assessed using the EQ-5D-5L questionnaire. This questionnaire gives insight in the patient's perception of their health-related QOL, this could possibly influence their satisfaction of the anti-tremor orthosis.

7.4 Withdrawal of individual subjects

Subjects can leave the study at any time for any reason if they wish to do so and revoke their consent without any consequences. The investigator can decide to withdraw a subject from the study for urgent medical reasons or in case the neurologist deems the patient not capable of participation for any physical or psychological reason.
In case of withdrawal, all patient data that was gathered during the course of the investigation will be – if possible - anonymized for privacy reasons.

7.5 Replacement of individual subjects after withdrawal

Depending on the number of subjects that are recruited, withdrawal of a patient will either lead to replacement of the subject or not. In case the sample size drops due to withdrawal, new patients will be included. We do not expect a high drop-out rate, since the study is not time consuming or demanding a lot of effort from a patient, nor are big risks associated with participation.

7.6 Follow-up of subjects withdrawn from treatment

Subjects that withdraw from the study, will not be followed or contacted for future research. Data that was already collected until the moment of withdrawal, will be used for the study.

7.7 Premature termination of the study

The study will terminate before finishing only in highly exceptional cases when:

- the judgment of the METC that assessed the investigation is irrevocably withdrawn.
- it is plausible that the research should be terminated in the interests of the health of the subjects.
- it appears that continuation of the study serves no scientific goal and that the METC confirms this.
- one of the parties is declared bankrupt or when bankruptcy is demanded.
- the principal researcher is no longer capable of performing the tasks he is assigned to and no replacement with mutual consent can be found.
- one of the parties do not fulfil the obligations as stated in the agreements and these obligations are not fulfilled after 30 days after receipt by the failing party of a written request for fulfilment.

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8. SAFETY REPORTING

8.1 Temporary halt for reasons of subject safety

In accordance to section 10, subsection 4, of the WMO, the sponsor will suspend the study if there is sufficient ground that continuation of the study will jeopardise subject health or safety. The sponsor will notify the accredited METC without undue delay of a temporary halt including the reason for such an action. The study will be suspended pending a further positive decision by the accredited METC. The investigator will take care that all subjects are kept informed.

8.2 AEs and SAEs

8.2.1 Adverse events (AEs)

Adverse events are defined as any undesirable experience occurring to a subject during the study, whether or not considered related to the investigational product or trial procedure. All adverse events reported spontaneously by the subject or observed by the investigator or his staff will be recorded using the *Adverse Event (AE) report form* (Dutch: meldingsformulier) that can be found in Appendix II.

8.2.2 Serious adverse events (SAEs)

A serious adverse event is any untoward medical occurrence or effect that

- results in death;
- is life threatening (at the time of the event);
- requires hospitalisation or prolongation of existing inpatients' hospitalisation;
- results in persistent or significant disability or incapacity;
- is a congenital anomaly or birth defect; or
- any other important medical event that did not result in any of the outcomes listed above due to medical or surgical intervention but could have been based upon appropriate judgement by the principal investigator.

An elective hospital admission will not be considered as a serious adverse event.
The investigator will report all SAEs to the sponsor without undue delay after obtaining knowledge of the event. The sponsor will report the SAEs through the web portal ToetsingOnline to the accredited METC that approved the protocol, within 2 days of first knowledge for SAEs that result in death or are life threatening followed by a period of maximum of 2 days to complete the initial preliminary report. All other SAEs will be reported within a period of maximum 5 days after the sponsor has first knowledge of the serious adverse events.

8.3 Follow-up of adverse events

All AEs will be followed until they have abated, or until a stable situation has been reached. Depending on the event, follow up may require additional tests or medical procedures as indicated, and/or referral to the general physician or a medical specialist.
SAEs need to be reported till end of study within the Netherlands, as defined in the protocol

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8.4 Data Safety Monitoring Board (DSMB)

Does not apply to this study.

9. STATISTICAL ANALYSIS

9.1 Primary study parameters

The primary objective of this study is to evaluate the effects of the STIL anti-tremor orthosis on the tremor severity and amplitude in the forearm.

Tremor severity using TETRAS

Tremor severity is assessed by the neurologist in 7 rated TETRAS[9] tasks using TETRAS' rating scale. This endpoint scores will be compared over the two conditions (baseline vs. intervention & sham vs. intervention).
A two-tailed matched pairs t-test will be used to analyze differences in tremor severity over these conditions.
First, the data will be tested for normal distribution. Then, the t-test will be applied to check for a difference in tremor severity in the two conditions. If the data is not normally distributed, 4 Wilcoxon matched pair tests will be performed. In this way, not only can the effects of the intervention be validated, but also the effects of the sham device (e.g. the effect of weight of the orthosis on tremor severity).

Tremor amplitude using IMU data

Tremor amplitude is measured during the performed tasks by taking the data from the IMU that is attached to the fingers. Likewise, this endpoint score will be compared over the two conditions using two-tailed matched pairs t-test, to analyze the difference in tremor amplitude. Again, the data will be checked for normal distribution, and the effect of the sham device will be evaluated.

The mean reduction in tremor severity according to both TETRAS rating and tremor amplitude of the hand are the co-primary endpoints. Sub analyses will be performed to evaluate the effect of the orthosis on these endpoints during the different tasks. This will be done to analyze the effect of the orthosis on specific tremor types: kinetic tremor (eating, drinking, pouring and spiral drawing), postural tremor (forward outstretched posture, lateral wing beating posture) and intention tremor (finger-to-nose).

9.2 Secondary study parameter(s)

Patient satisfaction using D-QUEST

The secondary study parameter 'patient's satisfaction' will both be assessed after the sham device and anti-tremor orthosis with the D-QUEST questionnaire. A sub-analysis per question will be performed, depicting the percentages of the total amount of patients that belong to one categorical measure (e.g., *very satisfied*, *not satisfied*).

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Potential adverse effects

All potential adverse effects – obtained from both the AEs reported from by investigator and sub-questions in D-quest – will be listed with their prevalence per patient (e.g. 15% of participants displayed skin marks).

9.3 Other analysis

Tremor amplitude will be analyzed separately for the wrist flexion-extension and forearm pronation-supination, by making use of the data collected on both IMU sensors. This will also be used to evaluate tremor amplitude reduction per DoF, and per task.

Moreover, the health-related quality of life – using the EQ-5D-5L – will be used to determine if the perceived quality of life could have effect on the patient satisfaction from the secondary study parameter(s). A sub-analysis per category (*Mobility/Self-care/Usual Activities/Pain & Discomfort/Anxiety & Depression*) will be assessed per participant compared to the results obtained from D-QUEST.

9.4 Prevention of missing data

Missing data will be prevented by checking all questionnaires on completeness and correctness before the patient leaves. To correct for missing data in questionnaires, missing data will be substituted by the weighted average. When data points of IMU sensors are missing, this will be substituted by making use of interpolation. If a patient is not able to perform a certain task, this will result in a complete missing data set from the IMU sensors and TETRAS score. That specific task for this specific subject will not be used in the data analysis. When two tasks or more cannot be performed, the data from the subject will be removed from the analysis.

9.5 Interim analysis

Does not apply to this study.

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10. ETHICAL CONSIDERATIONS

10.1 Regulation statement

This study will be performed in accordance to the principles of the declaration of Helsinki as written by the WMO in 2013 (version 64) and according to the WMO.

10.2 Recruitment and consent

- ET patients that are registered at the hospital will be informed about the study. The principal investigator, and other neurologists within the hospital, will identify ET patients that might be suitable for the study, such as patients who visited the hospital for consultation. The treating physician can call the patient to inform them about the study if he/she thinks that this patient is suitable. Additionally, CTcue will be used to screen patients who otherwise would have been overlooked.
- A brochure will be used to recruit additional eligible patients outside of the hospital. This brochure will be shared via (social) media and via affiliated neurologists from other Dutch hospitals. ET patients screened through this screening method can themselves contact the investigator(s) directly for more information, without any referral from their physician. To filter out requests, the investigator will ask a few elementary questions from the inclusion criteria (e.g.: "Are you diagnosed with ET") to validate if patients should receive a formal patient information form (PIF). The investigator will consequently send the selected patients the PIF with an application form by mail. The PIF also contains a cover letter that explains why patients received this invitation.
- If a patient is willing to participate, he/she fills out the application form and sends it back. Patients are requested to return the forms within two weeks.
- Patients who did not return the form within two weeks, will be contacted with a reminder letter.
- If additional questions arise, patients can always contact the investigators or the independent physician.
- Patients who fulfil all the inclusion criteria will be contacted by the investigator, to schedule an appointment for the inclusion test. This will be done with a phone conversation, during which patients can ask additional questions.
- Patients that are not eligible will receive a phone call that they will not be able to participate. The investigator is then also able to answer additional questions.
- The patient and investigator will sign the informed consent at the start of the appointment in the hospital. If, due to the severity of the tremor, the patient is unable to sign the informed consent, a representative person will sign it for them. The informed consent covers both the inclusion tests as the intervention with the orthoses (see Section 7.3.1).

10.3 Objection by minors or incapacitated subjects

Does not apply to this study.

10.4 Benefits and risks assessment

Since this will be the first clinical trial with the STIL anti-tremor orthosis and patients, no facts about risks and advantages are already known. Therefore, this summary lists the most important *possible* advantages and risks of the device.

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Advantages

No direct therapeutic effects are expected in this study. We expect that the orthosis will attenuate the tremor of the patient. It does not cure the disorder, but suppresses the tremor when the orthosis is mounted. Patients are not allowed to keep the orthosis after the intervention, since it is not the final product and no CE certification is yet obtained. We do not expect that the effects of the device will last after use.

When the orthosis is on the market and can be used by patients, major advantages for patients with forearm tremor are expected:

- Tremor reduction will have a big impact on the patient's activities of daily life and their social life. Activities they were avoiding or no longer capable of because of the tremor, will be possible again with the orthosis. This will make life a lot easier and comfortable.
- Patients suffering from side-effects of tremor medication, might be able to reduce the amount of medicines taken or potentially even able to stop altogether.
- Together, this will increase the quality of life of the patient.

Risks

In case the orthosis functions as supposed to, no severe adverse events are expected. The included patients are not a high-risk population, the orthosis only interacts with intact skin of the arm and hand and will be worn for a maximum of 1 hour (plus another hour for the sham device). Besides, precautionary measures are taken to prevent any risks caused by the orthosis in case of malfunctioning (as explained in section 12 and in the IMDD).

The orthosis is designed in such a way that only safe (bio-compatible) materials interact with the skin. Still, there is a possibility that the orthosis is not comfortable, which could possibly cause transient redness, itchiness, muscle pain or tendon irritation.

In case the orthosis does not function properly, the orthosis can be directly be detached by pulling the designated tabs for quick removal. No risks are expected with regards to the tasks and measurements that will be done in this study. The IMU sensors that will be used imply no additional risk.

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10.5 Compensation for injury

Reinier de Graaf hospital and STIL have a liability insurance which is in accordance with article 7 of the WMO.

Reinier de Graaf hospital also has an insurance which is in accordance with the legal requirements in the Netherlands (Article 7 WMO). This insurance provides cover for damage to research subjects through injury or death caused by the study.
The insurance applies to the damage that becomes apparent during the study or within 4 years after the end of the study.

Insured amounts
A1 € 650.000,= as maximum per claim per subject, with a maximum of
A2 € 5.000.000,= per single medical research, with comprehension that in case the institution conducts of have conducted multiple scientific researches, the total insured amount is limited to
A3 € 7.500.000,= for damage caused by scientific research per insurance year.

Exclusions regarding the test subjects
The insurance does **not** cover the following damage:

- damage due to a risk of which the patient has been informed in the written information. This does not apply if the risk is more serious than expected or if the risk was very unlikely to happen;
- health damage that would have occurred even if the patient had not participated in the study;
- damage caused by not (fully) following instructions;
- damage to offspring, as a result of a negative effect of the study on the patient or his / her offspring;
- damage caused by an existing treatment method when investigating existing treatment methods.

10.6 Incentives

Patients will receive €0.19 per km for round trip traveling expenditures and parking costs, or the price of public transportation. Patients that are excluded after the inclusion session in the hospital are also entitled to the travel reimbursement.

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11. ADMINISTRATIVE ASPECTS, MONITORING AND PUBLICATION

11.1 Handling and storage of data, documents and devices

Clinical investigation data means all data that was obtained during the study, including digital motion data (captured by the Xsens sensors), digital video data (captured by the webcams), digital notes of the investigator and digital questionnaires.
The only physical documents that are stored in this clinical investigation are the informed consents, the questionnaires during the inclusion protocol, and the questionnaires to validate user satisfaction.

11.1.1 Patient pseudonymization

Throughout the clinical investigation, involved patients will be pseudonymized; i.e. their name will be coupled to a random 3-digit number. This accounts for all patient that are in any way involved in the investigation:

- Patients that are selected for screening.
- Patients who are invited for the inclusion.
- Patients who are invited for testing.
- Patient that drop out during any of the above-mentioned steps.

The investigator(s) are the only ones who have access to the translation key. It is the responsibility of the principal investigator to safeguard the key throughout – and after – the clinical investigation.
In case needed, the monitoring committee may have access to the non-pseudonymized data as well. All other concerned staff will only have access to the pseudonymized data.

11.1.2 General procedure for handling and storing data and documents

Several general procedures are in place for handling and storing data and documents, in which hardware and software are involved.

- Hardware
  A hospital laptop with encrypted hard drive will be used for running the clinical investigation CRF software and collecting the patient data. The laptop is not connected to the hospital's network, nor the internet. If the laptop is not used, it will be stored in a closed locker. Throughout the clinical investigation, all motion and video data will remain on the laptop, as a backup. After the clinical investigation, the laptop drive will be formatted.
  After each testing, data will be transferred from the laptop, on to the hospital network. For his, an encrypted USB drive will be used. Data is copied to the USB drive, then inserted on a PC that is connected to the network. Data will then be copied to a location on the network only accessible to the investigators. Directly after the data transfer, the transferred data is removed from the USB drive
  No data can be stored on the anti-tremor orthosis, nor the motion sensors.
- Software
  A custom software package – the clinical investigation CRF – is developed to simultaneously capture motion and video data, but also to store the notes of the investigator in a log file. The software is only installed on the laptop of the sponsor, that is used solely for, and during, the clinical investigation. The CRF software will store the data on the laptop's encrypted hard drive.

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The collected clinical data (excluding the video and motion data) is also stored within the clinical evaluation software environment, Castor EDC (eCRF), governed by the sponsor. No information from the electronic medical record (Dutch: EPD) is needed. Patients will stay pseudonymized using the 3-digit ID number, and all data will be stored using this code. Data will be processed and stored conform the (AVG) procedures and policies of the Reinier de Graaf hospital, such as two factor authentication before being able to logon to the hospital network and data breach procedures.

- Documents
  Hard copy files (e.g. informed consents and questionnaires) will be stored for 15 years in a closed cabinet.

11.1.3 Procedures for handling and storing data and documents during the investigation

The following sections describe the handling and storage of data and documents for specific stages of the investigation.

- Inclusion procedure
  The inclusion questionnaire and informed consent that were collected during the inclusion procedure will be stored at the hospital in a locked cabinet. Only the investigator(s) will have access to these hardcopy files.
  The motion data and videos gathered during the inclusion procedure will be labelled with the 3-digit ID. After each inclusion session, all encrypted video data is transferred to the secured hospital network drive. All questionnaire data, and other commentary from the investigator, is stored in Castor EDC.

- Study procedure
  The videos collected during the study procedure will, again, be stored on an encrypted hard drive. Videos will only be viewed at the hospital's location. These videos can be consulted in case abnormalities have been observed in the TETRAS rating by the principal investigator. The tremor will be rated using TETRAS, the random 3-digit code will be used to assign the scores to the patients. Collected motion data will be pseudonymised and will only use the randomly assigned 3-digit ID code to connect them to the patient.
  The IMU/video data will be saved as followed: ID code_task_condition (e.g. 313_Eating_Baseline).
  The D-QUEST questionnaire will contain no names or any other information which could directly lead to the patient, it will again make use of the 3-digit code. This hardcopy file of the questionnaire will be stored at a secure site of the hospital. All the keys used during this phase will again be safeguarded by the principal investigator.

- Data analysis
  Analysis of the clinical investigation data will primarily be executed by the principal investigator on the laptop.
  In case expert input needs to be gathered outside of the institution, pseudonymized motion data can be transferred via an encrypted USB device. Motion data cannot be traced back to the patient.

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Only under supervision of the principal investigator may the video data be viewed by authorized persons/external experts, and only at a secure site within the hospital. Video data will never leave the premises of the hospital.
After the data analysis is completed, or at maximum two years after the last patient test, all digital data will be anonymised by deleting the translation key. Digital data that cannot be anonymised, such as the video's recordings, will be removed from the secure network drive. Anonymised data will be stored for 15 years.

11.1.4 Handling and storage of investigational devices

Accountability regarding the devices is documented by the principal investigator (or authorized designee), in particular control of access to the devices, follow-up with regard to the devices used in the clinical investigation and the return of unused, expired or defect devices. The investigational devices shall only be used in the clinical investigation and according to the CIP.
If the devices are not used, they will be stored in their casing, in a locked cabinet.
The sponsor shall keep records to document the physical location of all investigational devices from shipment to the investigation sites until return of disposal. Both the sponsor and principal investigator (or authorized designee) can make use of the Dutch version of the *Device Accountability Log* (Dutch: Verantwoordingsrapportage STIL's anti-tremor orthose) that can be found in Appendix III.

11.2 Monitoring and Quality Assurance

The monitoring committee that is assigned by the hospital will monitor this study. This will be done conform the CCMO rules. Prior to the start of the study, this committee will check if all requirements are met and if all documents are correct. After finishing, the study will be evaluated by the monitoring committee.

An initiation visit (or phone call, or other communication, if appropriate) must be conducted and documented by the sponsor or monitor at the beginning of the clinical investigation. Prior to initiation, the monitor must check whether principal investigator and investigation team:

- Received and understood contents of CIP, IB, informed consent, eCRFs and IFUs.
- Have access to adequate number of investigational devices.
- Have been trained adequately to use device.
- Are familiar with their responsibilities.

11.3 Amendments

All amendments will be notified to the METC that gave a favourable opinion.

11.4 Annual progress report

The investigator will submit a summary of the progress of the trial to the accredited METC once a year. Information will be provided on the date of inclusion of the first subject, numbers of subjects included and numbers of subjects that have completed the trial, serious adverse events/ serious adverse reactions, other problems, and amendments.

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11.5 Temporary halt and (prematurely) end of study report

The investigator/sponsor will notify the accredited METC of the end of the study within a period of 8 weeks. The end of the study is defined as the last patient's last visit.

The sponsor will notify the METC immediately of a temporary halt of the study, including the reason of such an action.

In case the study is ended prematurely, the sponsor will notify the accredited METC within 15 days, including the reasons for the premature termination.

Within one year after the end of the study, the investigator/sponsor will submit a final study report with the results of the study, including any publications/abstracts of the study, to the accredited METC.

11.6 Public disclosure and publication policy

The results will be published by the hospital once all study subjects have completed the study and the study has been analysed. The principal investigator shall submit any projected publication (including but not limited to press release, oral presentations and other publications reporting results or part of the results) to the manufacturer for review at least thirty (30) days prior to its submission, or at least ten (10) working days in case of an abstract ("Review Period"). The manufacturer will inform the principal investigator within the Review Period whether the proposed publication will adversely affect a patent or other rights of Company on proprietary information. If the manufacturer objects, the principal investigator and/or the hospital will delay publication or presentation for no longer than an addition 30 days to protect such interests and, if required, remove any manufacturer's proprietary information from the publication. The manufacturer recognizes that the principal investigator's and possibly hospital's objective is to expeditiously disseminate new scientific and technical knowledge. To this end, the manufacturer will take prompt action reasonably necessary to allow public disclosure without jeopardizing its patent or proprietary rights. If no reaction from the manufacturer has been received by the principal investigator within the term specified in this Agreement, the hospital can proceed with the publication without further delay.
More information on publication can be found in Section 5 of the research contract (K3).

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12. STRUCTURED RISK ANALYSIS

12.1 Potential issues of concern

a. Level of knowledge about mechanism of action

Tremor is a roughly sinusoidal involuntary vibration of a body segment [30]. The working mechanism is based on the principle of applying external joint damping. Two dampers are used to restrict high frequency involuntary motion, while having low impact on voluntary motion that is required for daily activities. The dampers are chosen based on the joint torque values in kinetic tremors and user testing with healthy subjects to suppress undesired motion but minimize the chance of obstructing voluntary motion too much. A more detailed description can be found in Section 1.1 of the IMDD.

b. Previous exposure of human beings with the test product(s) and/or products with a similar biological mechanism

A prototype of the orthosis has been tested in an internal feasibility study to test the safety, comfort and hygiene of the orthosis; a more detailed description of this test can be found in Section 6.2.

A device with a somewhat comparable working principle is the Steadi-One, a non-invasive passive device using tuned mass dampers (TMD) to suppress tremor, which uses a non-Newtonian fluid to reduce the amplitude of motions. However, the way tremor is suppressed differs substantially from the STIL anti-tremor orthosis.

c. Can the primary or secondary mechanism be induced in animals and/or in *ex-vivo* human cell material?

Does not apply to this study.

d. Selectivity of the mechanism to target tissue in animals and/or human beings

Does not apply to this study.

e. Analysis of potential effect

The orthosis is equipped with passive dampers which exert an additional damping to the respective joint. In this manner, high frequency involuntary movement, such as tremor, is suppressed but voluntary motion is still allowed. This will have a positive effect on the functional and social life of the patient.

The orthosis is made as save as possible, by implementing precautionary measures in order to minimize the risks for the patient. The following list consists of possible situations with a high-risk index value, which are generally unacceptable, that could occur during the clinical trial. After performing the precautionary measures, the residual risk index value could be considered acceptable. A more detailed list of precautionary measures to avoid hazardous situations is conducted in Appendix VI of the IMDD.

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I. The user appears to be allergic to a certain substance present in the device, triggering an allergic reaction, which could possibly result in redness of the skin of even the need for medication.

Precautionary measures:

1. The device is entirely made of biocompatible materials, including lubrication grease and oils.
2. Plastic components are made of medical grade quality.

II. When heavy weight is applied on top of the hand piece, or when it is forcefully shaped into a new shape, there is a possibility that the hand piece could plastically deform, which is particularly dangerous if a metal insert is included in the hand piece. This could lead to bruising and discomfort.

Precautionary measures:

1. Plastic components are made of medical grade quality.
2. The hand piece comes in different sizes to ensure a well-suited fit for the vast majority of patients.
3. The hand cuff is designed in a way that it cannot plastically deform in a way that it could clamp the hand

III. When performing eating/drinking activities, it is required to bring possible sharp utensils or cups close to the mouth in order to eat/drink. This could result in minor damage to the mouth, lips, teeth or gums.

Precautionary measures:

1. As this risk is mainly controlled by the caution of the user, they can primarily only be alerted to the risk. Furthermore, this risk is limited by avoiding sharp utensils, such as cutting knives.

f. Pharmacokinetic considerations

Does not apply to this study.

g. Study population

Subjects (18+) have significant difficulties in daily activities due to their forearm tremor and are diagnosed with ET, which is the most common movement disorder which exhibits tremor. Patients have a stable condition and all the other criteria exclude more vulnerable patients. Women of childbearing age are eligible, since the effects of wearing the orthosis for about 1 hour will not have a negative influence on fertility. However, pregnant women are excluded from participation. The effect of the STIL anti-tremor orthosis on the embryo is unknown and even though the risk for side-effect may be extremely low, no risk will be taken.

h. Interaction with other products

Patients with an implanted electrical deep brain stimulator are excluded from participation, as the effect of the STIL anti-tremor orthosis on a tremor treated with DBS is unknown. Patients are

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allowed to take prescribed medication. In this study, no substances will enter the body but only additional damping to the respective joint will be exerted. This will not interact with medication as it is external. However, patients are asked not to change their medication in the 30 days prior to the study. As for antidepressants, no change in the 90 days prior to the study apply.

i. Predictability of effect

Based on the risk analysis, minimal adverse effects are expected with this study. We hypothesize that the orthosis will decrease the tremor *amplitude* with 60% or more and reduce tremor *severity* by one ordinal measure on the TETRAS scale (e.g. from moderate to slight tremor).
In this study, the long-term effect of the STIL anti-tremor orthosis will not be investigated, as the orthosis will be worn for 30 minutes. We expect however, when the orthosis reduces tremor severity significantly, that this could have a major positive influence on ADL and QoL on the long run.

j. Can effects be managed?

The device can only successfully suppress tremor when the tremor is present, the damper is not utilised when there is no tremor present. When unsafe or uncomfortable situations arise, the patients may be asked to rest their arms on the table. In this position, most ET patients do not exhibit a tremor. Another way to control the effect, is to detach the orthosis directly using the designated pulling tabs which allow for quick removal.

12.2 Synthesis

Based on the exhaustive risk analysis in the IMDD, where hazard, risks and risk control measures are weighted, we conclude that the overall risk for this study is low.
Because of the implemented safety measures, hazardous situations caused by the device are very unlikely to happen. Moreover, the orthosis will be worn for a maximum of 30 minutes (an additional 30 minutes for the sham device) and can be detached directly in case of emergency. Together with the inclusion and exclusion criteria, the included patients are at low risk and in a condition that is healthy enough to participate. Taken together, this results in an overall low risk of this study.

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APPENDIX I - INSTRUCTIONS ON HOW TO EVALUATE TREMOR PER DOF

TETRAS makes use of different rating scales to rate tremor in different tasks. *Figure 8* displays the three different scales used to assess the tasks relevant to STIL. Tasks consist of the forward outstretched posture, lateral "wing beating" posture, finger-to-nose manoeuvre, spiral drawing, pouring, drinking and eating.

Every posture and ADL task will be scored using the *upper limb tremor scale*. Also, all the different DOFs will be assessed using this scale. Instructions can be found on the next pages, distance between movements is absolute. The ADL tasks will also be scored using the *ADL task scale*, to assess the performance of the exercise.

To assess the spiral drawing, the *spiral scale* will be used. In the video footage two spirals are shown, only assess the first bigger spiral. The scores are defined by whole numbers. However, 0.5-point increments may be used it a rating cannot be reconciled to the higher or lower whole number.

Use *figure 9* to fill out your scores.

	RATING SCALE		
Score	**Upper limb tremor**	**Spiral**	**ADL tasks**
0	None	Normal	Normal
0.5	-		
1	< 0.5 cm	Slight; barely visible	Slighty abnormal; presen but does not interfere
1.5	0.5 - < 1 cm		
2	1 - < 3 cm	Mild; obvious tremor	Mildy abnormal; some difficulty but can complete tasks (little spill)
2.5	3 - < 5 cm		
3	5 - < 10 cm	Moderate; parts not recognizable	Moderately abnormal; big spill, change of strategy
3.5	10 - < 20 cm		
4	≥ 20 cm	Severe; figure not recognizable	Severely abnormal. Cannot do it

Figure 8: TETRAS scales

Patient

Scale	Upper limb tremor						Spiral	ADL tasks		
Item	Streched	Wing	Nose	Pouring	Drinking	Eating	Spiral	Pouring	Drinking	Eating
Overall										
SIER										
EFE										
FPS										
WFE										
FFE										

Figure 9: Scoreform

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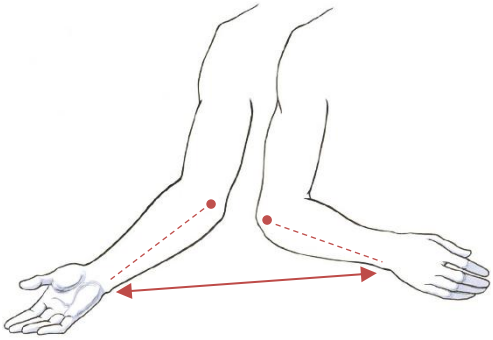
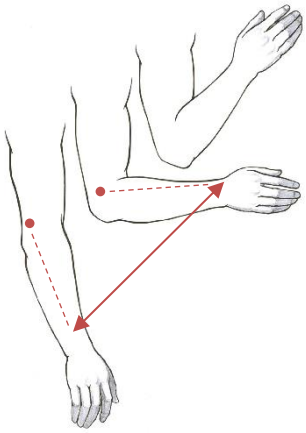
HOW TO ASSESS THE DIFFERENT DOFs AND WHAT TO PAY ATTENTION TO

SHOULDER INTERNAL/EXTERNAL ROTATION (SIER)

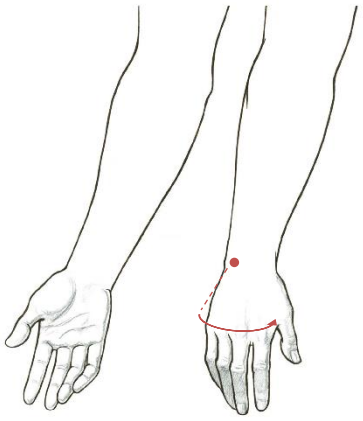
Here you look at the biggest movement of the wrist in relation to the elbow, focus on the same spot of the wrist when the upper arm rotates. This is the movement that is perpendicular to the upper arm.





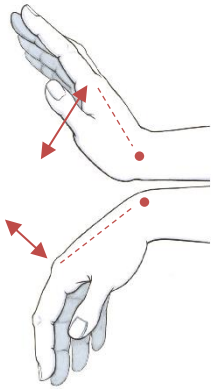
ELBOW FLEXION/EXTENTION (EFE)

The vertical movement of the wrist in relation to the elbow in flexion/extension of the elbow.
Not to be confused with a SIER when the upper arm is lifted.



FOREARM PRONATION/SUPINATION (FPS)

With pronation and supination of the forearm, you look at the knuckle that shows the largest movement. Here, interference from WFE and FFS can cause difficulty. Measure the largest absolute distance you observe.

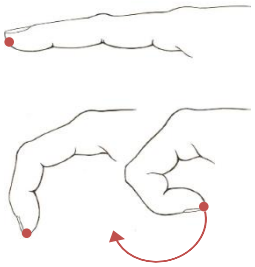


WRIST FLEXION/EXTENSION (WFE)

For flexion/extension of the wrist joint, we take the knuckle that is furthest from the wrist as a reference point. Here too, the FFE can cause difficulties. Measure the largest absolute distance you observe.

FINGER FLEXION/EXTENSION (FFE)

To evaluate the fingers, you need to look at the finger furthest from the hand. In most cases, this will be the middle finger. Observe what the biggest movement from tip to tip is and derive the absolute distance from one point to the other.



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APPENDIX II – Adverse Event (AE) Report Form (Meldingsformulier)

NL79108.000.21

Adverse Event (AE)
Meldingsformulier

ONDERDRUKKING VAN ONDERARM TREMOR MET DE STIL ANTI-TREMOR ORTHESE

Protocol ID:_____

Patiënt ID:_____

Dit formulier is cumulatief en legt de bijwerkingen van een enkele deelnemer tijdens het onderzoek vast.

Ernst	Relatie met de studie interventie	Ondernomen actie betreft interventie	Resultaat van AE	Verwacht	Serious Adverse Event (SAE)
1 = Mild 2 = Matig 3 = Ernstig 4 = Levens-bedreigend	1 = Geen 2 = Onwaarschijnlijk 3 = Mogelijk 4 = Waarschijnlijk 5 = Zeker	0 = Geen 1 = Dosisaanpassing 2 = Medische interventie 3 = Ziekenhuisopname 4 = Interventie stopgezet 5 = Anders	1 = Opgelost 2 = Hersteld met kleine gevolgen 3 = Hersteld met grote gevolgen 4 = Waarschijnlijk 5 = Doorgaan behandeling Verslechtering van toestand 6 = Dood 7 = Onbekend	1 = Ja 2 = Nee	1 = Ja 2 = Nee (Indien ja, melden via *ToetsingOnline*)

Alleen aan het einde van de studie: Vink dit vakje aan als de deelnemer geen bijwerking had ☐ **Geen**

Adverse event	Ernst	Relatie	Ondernomen actie	Resultaat van AE	Verwacht?	SAE?

AE Meldingsformulier

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APPENDIX III – Device Accountability Log (Verantwoordingsrapportage STIL's anti-tremor orthese)

NL79108.000.21 Onderdrukking van onderarm tremor met de STIL anti-tremor orthese

Verantwoordingsrapportage STIL's anti-tremor orthese

Ontvangst					Gebruik				Dispositie (Retourneren/Reparatie/Vernietiging)					
Datum ontvangst	Apparaat type (sham of interventie)	Serienummer [TEST01]	Ontvangen door (initialen personeel)	Plaats (alleen voor de sponsor)	Datum gebruik	Patiënt ID	Afgegeven door (initialen personeel)	Plaats (alleen voor de sponsor)	Status RET=Retour VERN=Vernietigd REP=Gerepareerd VERL= Verloren AND= Anders (verplicht)	Datum dispositie	Reden (studie voltooid, ingetrokken, niet opgevolgd, verlopen/beschadigd apparaat, niet functionerend of teruggeroepen)	Plaats (alleen voor de sponsor)	Bevestigd door (initialen personeel)	Opmerkingen

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