Protocol

Occipital nerve stimulation in medically intractable, chronic cluster headache

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1. Summary

Cluster headache (CH) is a primary headache disorder characterized by recurrent short-lasting attacks (15 to 180 minutes) of excruciating unilateral periorbital pain accompanied by ipsilateral cranial autonomic signs (1). The 1-year prevalence of CH is about 0.1 %, the male: female ratio is 3:1. The majority of patients have cluster periods of weeks to months with frequent attacks which are alternated with symptom-free periods of months to several years; the episodic from of CH. In about 10% of patients the CH is chronic (CCH) in which either no remission occurs within 1 year or the remissions last less than 1 month. At least 10 % of CCH patients are refractory to medical treatment or cannot tolerate the treatments (2).

Recent pilot studies suggest that occipital nerve stimulation (ONS) in medically intractable CCH (MICCH) might offer an effective alternative to medical treatment. There are no randomised clinical trials and a placebo effect cannot be excluded. Long term tolerability is known from other indications.

Here we propose a prospective, randomised, double blind, parallel group multi-centre international clinical study to compare the reduction in attack frequency from baseline of occipital nerve stimulation (ONS) in patients with MICCH between two different stimulation conditions: high (100%) and low (30%) stimulation.

Following implantation there will first be a run-in phase of 10 days of 10% stimulation intensity, followed by a stepwise monthly increase up to either 30% or 100%. Patients will be assessed monthly by a blinded assessor. The primary outcome measure is the mean number of attacks over the last 4 weeks of the double blind 6 month treatment period in the 100% versus the 30% treatment group. Hereafter, in an open extension phase of 6 months, all patients will receive 100% stimulation or the stimulation considered optimal by the patient.

Secondary outcome measures include the rate of responders (≥ 50% reduction in attack frequency during the last 4 weeks of each treatment period), patient's satisfaction, medication use, quality of life, mean pain intensity, economic evaluation

and whether patients would recommend the treatment to another patient. We will also investigate whether predictive factors can be identified for efficacy.

2. Background

2.1 Cluster headache

Trigeminal autonomic cephalalgias (TACs) are characterized by frequent, short-lasting attacks of unilateral extremely severe headaches accompanied by ipsilateral facial autonomic features and are the most severe of the primary headache disorders (1). TACs include cluster headache (CH), paroxysmal hemicrania (PH) and short-lasting unilateral neuralgiform headache with conjunctival injection and tearing (SUNCT) (3;4). CH is the most common form of TAC. The 1-year prevalence is about 1 in 1000, with the vast majority of patients having episodic CH (ECH): periods of weeks to months with frequent attacks which are alternated with symptom-free periods of several months to years. About 10% have chronic CH (CCH): attack free periods of less than one month in every 12 months, unless treatment is given. The chronic form can be primary unremitting from onset, or can be secondary, transform from the episodic form. CCH may spontaneously become episodic.

2.2 Treatment

Effective acute treatments for CH attacks are injectable or intranasal triptans and oxygen inhalation. Steroids (only for a short period), verapamil, lithium carbonate and methysergide are the most effective preventive therapies. At least 10% of patients with CCH is or may become refractory to or cannot tolerate medical therapy. For patients with medically intractable CCH (MICCH) there is no common treatment. Different experimental treatments, such as deep brain stimulation (DBS), radiofrequency lesions, glycerol injections, gamma knife, and surgery or root section of the trigeminal nerve are either substantially ineffective, or have significant short-comings with serious complications such as death or neurological deficits such as anaesthesia dolorosa or lack of efficacy.

2.3 Social and economic impact

CH has considerable impact on socio-economic and personal functions due to direct costs of healthcare services and indirect costs of lost work days and decreased work

efficacy (5). Higher pain scores and a higher percentage of patients with poor health due to pain and social functioning are found among CH patients compared with patients suffering from migraine (6). The impact on social functions, quality of life and use of healthcare of patients with MICCH is most likely even larger, although precise figures are not available. In the study of Burns et al. (7) patients, suffering from MICCH, had on average over four attacks per day. Attacks of CH have been described by patients as being worse than child birth. Recently treatment of headache was listed as one of the top priorities of US National the Institute of Medicine's agenda for comparative-effectiveness research (8).

2.4 Hypothalamic deep brain stimulation

Functional imaging studies in CH identified activations in the region of the posterior hypothalamus, which led to the use of neurostimulation therapy in MICCH. Hypothalamic DBS was shown to be effective in some patients with MICCH but unfortunately this treatment is associated with a high risk of (even lethal) consequences (9-12).

2.5 Stimulation of the suboccipital nerve in CH

Structures in the occipital region of the head are mainly innervated by the greater occipital nerve that is a branch of the C2 spinal root. Convergence of cervical, somatic trigeminal and dural trigeminovascular afferents on second order nociceptors in the brain stem is well documented (13-16).

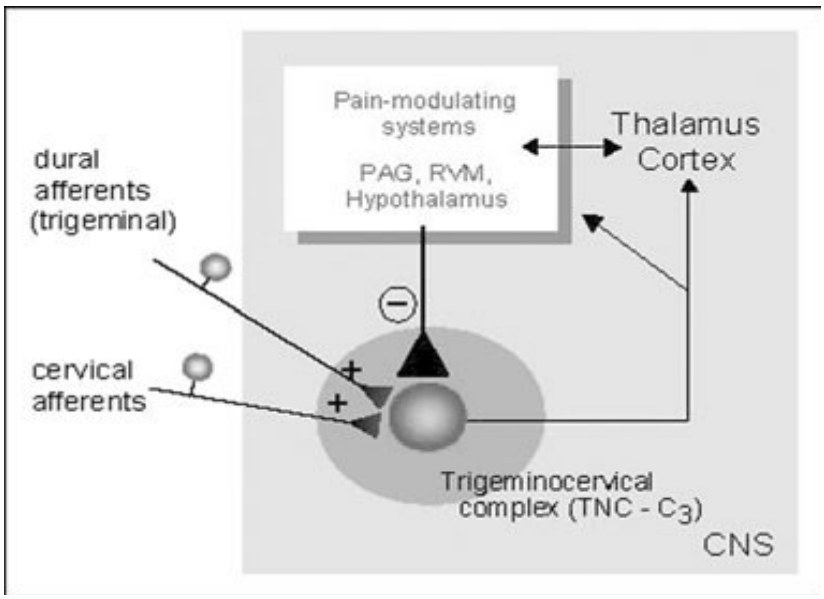


Figure.—Illustrated are the elements of the anatomy and physiology of
the trigeminocervical complex with both dural (trigeminal) and cervical
afferents projecting to thalamus and cortex.
Periaqueductal grey matter (PAG), rostroventral medulla (RVM), central nervous system (CNS).

Source: Occipital Nerve Stimulation for Headache:
Mechanisms and Efficacy
Goadsby P.J. et al., Headache, 2008, (16)

Stimulation of the greater occipital nerve increased metabolic activity in cervical regions of the spinal cord and in the trigeminal nucleus caudalis in the cat (14). In humans an occipital nerve blockade decreased the ipsi- and contralateral R2 response, confirming the anatomic and functional convergence of afferent cervical and trigeminal pathways (17). These studies suggest that modulation of these pathways may influence headache.

Suboccipital injection of corticosteroid with local anaesthetics was shown to be effective in a placebo-controlled trial (18). In this study 4 patients suffering from CCH were included. In all patients the attacks recurred eventually. The authors suggest that suboccipital steroid injections ought to be tried as a single shot treatment before invasive treatments are considered such as DBS, but in later studies this turned out to be of no predictive value of the response to neuromodulation therapies (9;19;20).

Along the same line, stimulation of the greater occipital nerve (ONS) has been tried with some success in intractable headaches including CCH (7;19-22). Burns et al. described 14 patients suffering from MICCH and were treated with ONS in an open retrospective study. Ten patients improved; three improved by 90% or more, 3 by 40%-90% and 4 by 20-30%. (7;23). In a prospective open ONS study on MICCH patients Magis et al. showed a reduction in attack frequency of 79.9% (20). No serious complications were described in both studies.

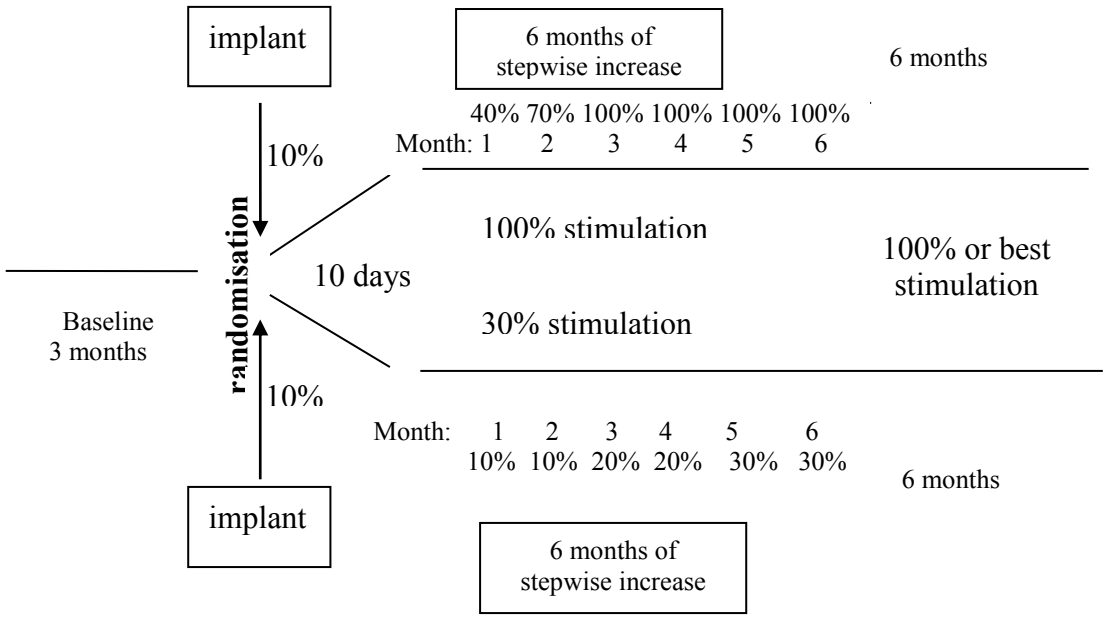
3. Study Rationale

There is no established treatment for patients with MICCH. ONS has been used in open label trials with promising results (7;19-22). A prospective, randomised, controlled clinical trial is necessary to assess the efficacy, tolerability and safety of ONS in the treatment of MICCH.

4. Study design

This is a prospective, randomised, double blind, parallel group multi-centre international clinical study to compare the reduction in attack frequency from baseline of occipital nerve stimulation (ONS) in patients with MICCH between two different stimulation conditions: high (100%) and low (30%) stimulation. (see paragraph 10.1)

Active ONS is associated with paraesthesias complicating blinded comparison versus no stimulation. From our own experience with patients treated with ONS, we know that patients might find it difficult to differentiate paraesthesias associated with 100% and 30% stimulation. Recognition of the stimulation intensity would be further complicated by stepwise increasing the stimulation intensity.



Patients will be included for a 3 month baseline period, of which the first month serves for practice only. If the patient still meets the inclusion criteria after this baseline period, he/she will be randomised and scheduled for surgery. Following surgical implantation there will first be a run-in phase of 10 days of 10% stimulation intensity until wound check, followed by a stepwise increase up to either 30% or 100%. Patients in the 100% stimulation arm will receive this intensity for 4 months.

Patients will be assessed every month by the blinded study neurologist. If the patient finds the stimulation painful in between follow-up moments, an extra follow-up moment will be arranged soon and the threshold for discomfort will be defined again. The primary outcome measure is the number of attacks over the last 4 weeks of the double blind 6 month treatment period. Hereafter, in an open extension phase of 6 months, all patients will receive 100% stimulation or the stimulation considered optimal by the patient. The patients will fill in an (electronic) diary during the whole study period.

Rationale design

We estimated the effect of ONS in three Dutch patients. We found that sensation threshold and discomfort threshold can be repeatedly defined and that patients could not distinguish small differences in stimulation.

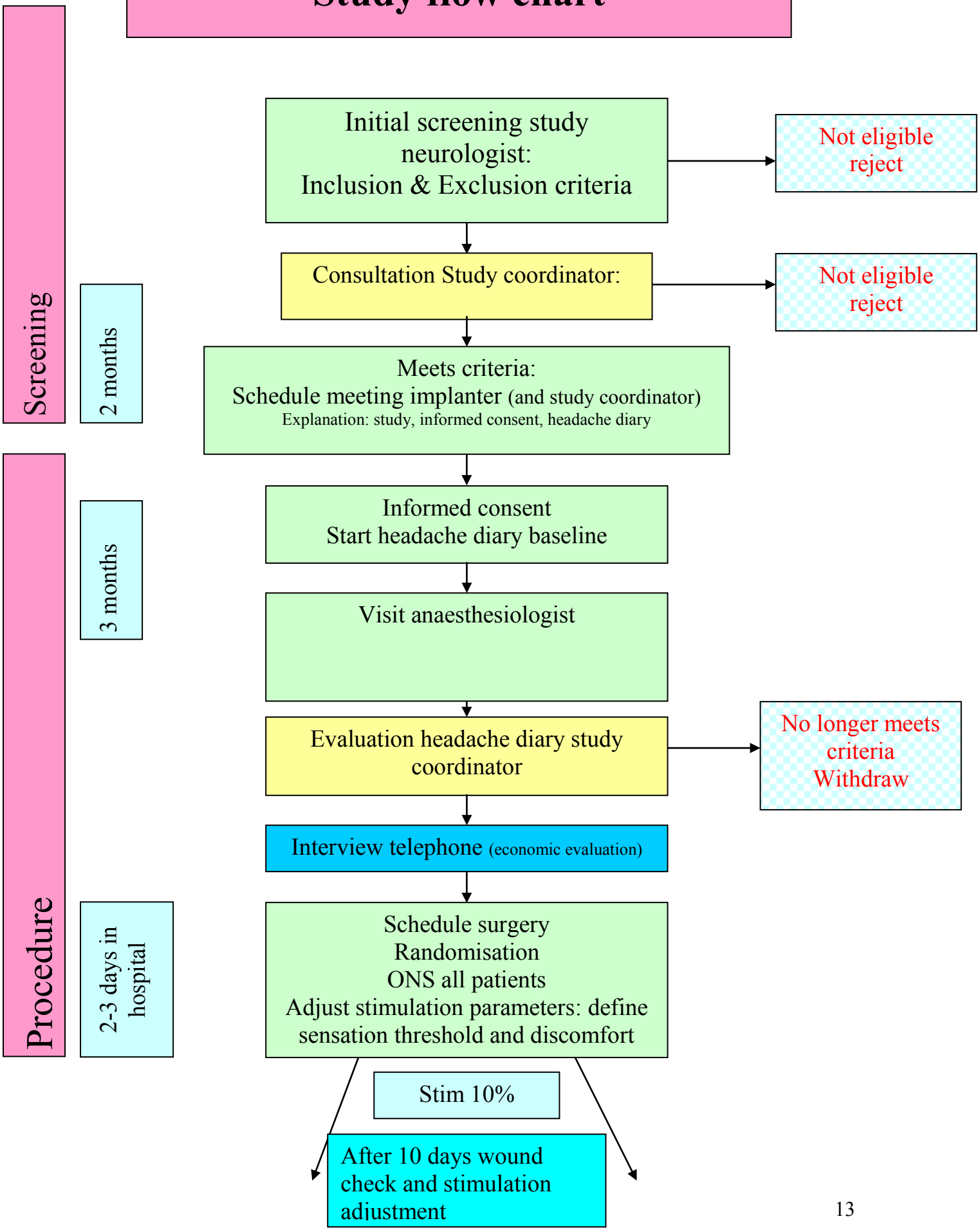
A similar design was successfully used in a multicenter, prospectively randomised, parallel, double-blind study that showed that high vagus nerve stimulation gave significantly more reduction in seizure frequency than low vagus nerve stimulation (24). This finding supports a proposed dose response in neurostimulation and subsequently supports our design. Supposed treatment allocation by the patient, on the other hand, was not mentioned in this study.

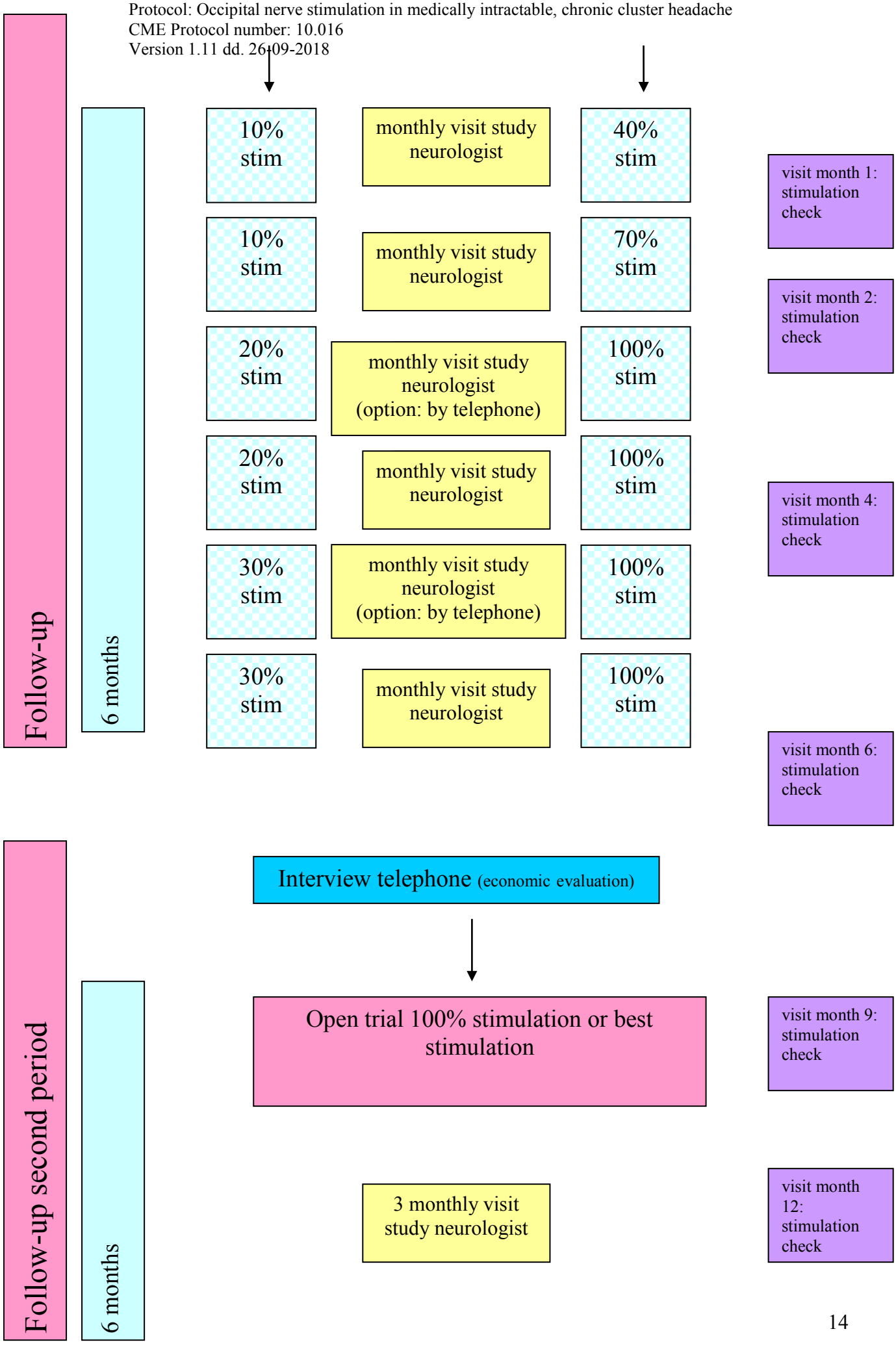
Matharu et al. (25) showed a correlation between mean pain scores, stimulator induced paresthesia and changes in regional cerebral blood flow in ONS treated chronic migraine patients. These findings suggest a dose related effect of the stimulation and thereby supports our design.

Blinding

Patients, neurologists and the study investigator will be blinded for the randomisation. The IPG programming (not blinded) will be performed by the implanter (neurosurgeon or anaesthesiologist) or research nurse. They will take precautions to ensure that patients are unaware of their randomisation status by not informing them about the stimulation conditions.

Study flow chart




Follow-up
6 months
10% stim
monthly visit study neurologist
40% stim
visit month 1: stimulation check
10% stim
monthly visit study neurologist
70% stim
visit month 2: stimulation check
20% stim
monthly visit study neurologist (option: by telephone)
100% stim
20% stim
monthly visit study neurologist
100% stim
visit month 4: stimulation check
30% stim
monthly visit study neurologist (option: by telephone)
100% stim
30% stim
monthly visit study neurologist
100% stim
visit month 6: stimulation check
Interview telephone (economic evaluation)
Follow-up second period
6 months
Open trial 100% stimulation or best stimulation
visit month 9: stimulation check
3 monthly visit study neurologist
visit month 12: stimulation check

	T=-3	T=-2	T=-1	T=0	T=1	T=2	T=3	T=4	T=5	T=6
	Inclusion start electronic diary	Pre-op 3 months after inclusion	Intervention	10 days after surgery	1 month after surgery	2 months after surgery	4 months after surgery	6 months after surgery	9 months after surgery	12 months after surgery
Visit Window				± 2 days	± 1 week	± 1 week	± 2 weeks	± 2 weeks	± 4 weeks	± 4 weeks
Patient characteristics	X									
Intervention			X							
Wound inspection			X	X						
Headache diary	X	X			X	X	X	X	X	X
Stimulation and system check			X	X	X	X	X	X	X	X
Economic evaluation questionnaire		X						X		
Patient satisfaction								X		X
Adverse events	X	X	X	X	X	X	X	X	X	X

5. Patient recruitment

Patients will be recruited from tertiary headache clinics in The Netherlands, Denmark, UK and probably Belgium and Germany.

6. Study Purpose

Objectives

The primary objective of this study is to investigate whether ONS reduces the attack frequency in MICCH compared to baseline.

7. Endpoints

7.1 Primary

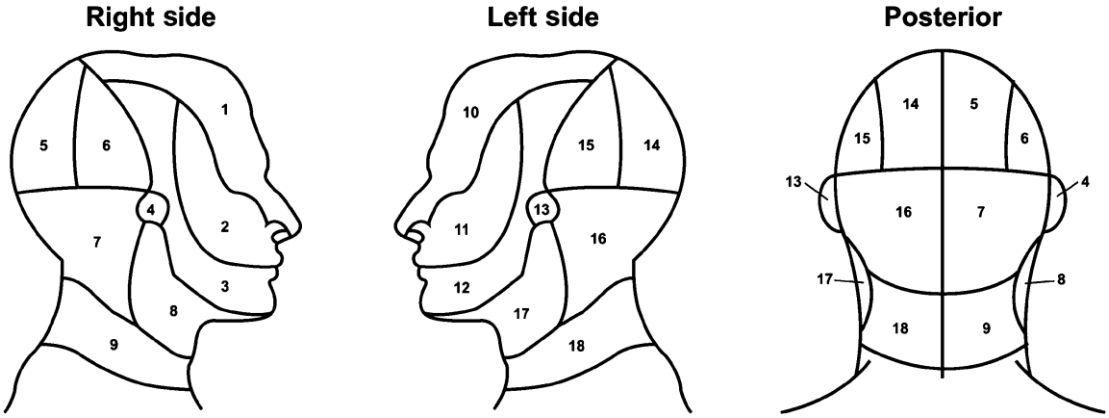
The primary endpoint is the mean attack frequency (MAF) over the last 4 weeks in the 100% and the 30% treatment groups at 6 months.
An attack is defined as any attack recognised by the patient as being a CH attack. So also the attacks treated with oxygen or triptans.
(For consistency of calculation, any reference in this document to a month shall mean a period of 4 weeks.)

7.2 Secondary

MAF: We will repeat the primary analysis, with the MAF as outcome instead of the logarithm of the MAF.
MAF during follow-up: The MAF for each 4 week period of the whole follow-up period.
Mean attack intensity: The mean attack intensity (on a scale from 0-10) will be calculated over the last 4 weeks for each group at baseline, 6 and 12 months follow up and will be compared between and within the 2 groups.
Responder rate: Rate of responders (>50% reduction in attack frequency in the last 4 weeks compared to baseline) will be calculated and compared between groups at 6 and 12 months.
Economic evaluation: see paragraph 11.

Anticipated group randomisation: The patient and assessors will be asked at 6 months follow-up (before deblinding), in which treatment group (high or low stimulation) they think the patient was allocated.

Awareness of paraesthesias: localisation and strength will also be evaluated weekly and coded through the patients' recordings in the electronic diary and compared with effectiveness of stimulation, e.g. frequency of attacks.



Picture used to code location of stimulation.

From: Stimulation Ranges, Usage Ranges, and Paresthesia Mapping During Occipital Nerve Stimulation
Trentman T.L. et al., Neuromodulation, 2008 (26)

The use of acute attack medication: The number of doses of sumatriptan injections or intranasal spray or O_2 inhalation periods will be investigated and calculated of the last 4 weeks of each treatment period and the baseline period, and compared between and within groups.

Patient satisfaction: We will ask the patient at 6 and 12 months follow-up whether he/she would recommend the treatment to another patient using a 5 point (Likert) scale: Strongly disagree, disagree, neither agree nor disagree, agree, strongly agree.

Responder identification: It is also investigated whether predictive factors can be identified with respect to the outcome in a hypothesis generating manner. We will look at the body mass index (BMI) and assess the predictive value of response after 5-7 days.

Adverse events: All and treatment-related adverse events will be documented by the investigators.

8. Patient Selection Criteria

Diagnosis of patients with CH shall be in accordance with *The International Classification of Headache Disorders, 2nd Edition: (1)*

A. At least 5 attacks fulfilling criteria B–D

B. Severe or very severe unilateral orbital, supraorbital and/or temporal pain lasting 15-180 minutes if untreated

C. Headache is accompanied by at least 1 of the following:

1. ipsilateral conjunctival injection and/or lacrimation
2. ipsilateral nasal congestion and/or rhinorrhoea
3. ipsilateral eyelid oedema
4. ipsilateral forehead and facial sweating
5. ipsilateral miosis and/or ptosis
6. a sense of restlessness or agitation

D. Attacks have a frequency from 1 every other day to 8 per day

E. Not attributed to another disorder

Chronic cluster headache

A. Attacks fulfilling criteria A–E for *Cluster headache*

B. Attacks recur over >1 year without remission periods or with remission periods lasting <1 month

8.1 Inclusion Criteria

- ICHD-II criteria for CCH *(see above)*
- Minimum mean attack frequency of 4 attacks per week
- Minimum age of 18 years old
- Signed study specific informed consent form agreeing to implantation of the device, data collection and follow-up requirements
- Agreeing to refrain from starting new prophylactic CH medication, including steroids, or any other therapy aimed at CH (such as acupuncture, biofeedback, chiropractic, or massage) and agrees to maintain existing prophylactic CH medication from 4 weeks before entering the baseline

period throughout the duration of the double blind phase of the study. It is allowed to change the dose of prophylactic medication during the study based on the opinion of the treating medical specialist.

- Availability during follow-up period
- An MRI not older than 4 years prior to enrolment must be available to exclude structural lesions potentially causing CCH. An exception can be realized by the study coordinator in case of stable CH for over 4 years and no change in symptoms after the last MRI scan was performed.
- MRA of head and neck are to be performed according to study physician's individual judgement.
- Medically intractable (see below)

Definition medically intractable :(2)

Failed adequate trials of regulatory approved and conventional treatments according to local national guidelines

Current prophylactic treatment of CH consists of corticosteroids (short term only), methysergide (short term only), verapamil and lithium. Other drugs, such as valproate, pizotifen, topiramate and gabapentin are also used without clinical evidence (27). Prolonged treatment with methysergide has been associated with fibrotic reactions and therefore is no longer available in the USA and some other European countries. Corticosteroids are often efficacious, but treatment should be limited to 6-8 weeks. For this reason patients do not have to be intractable for corticosteroids to be included in the study. Verapamil is the preventive drug of choice in CCH, followed by lithium (28).

Adequate trial:

Appropriate dose and duration of treatment according to local guidelines
Appropriate length of time
Consideration of medication overuse

Failed:

No therapeutic or unsatisfactory effect, intolerable side effects, contraindications to use

Must have tried agents of at least three classes of the following, of which 1 and 2 are obligatory, and 1 should come from 3-5: *(recommendation of Goadsby et al. applied to Dutch national guidelines)* (2)

1 Verapamil

2 Lithium

3 Methysergide

4 Topiramate

5 Gabapentin

8.2 Exclusion Criteria

- Other significant neurological or disabling diseases (including other forms of TAC) which in the opinion of the clinician may interfere with the study
- Pregnancy or the wish to become pregnant during the study period
- Cardiac pacemaker and other neuromodulatory devices
- Psychiatric or cognitive disorders and/or behavioural problems which in the opinion of the clinician may interfere with the study
- Taking CH prophylactic medication for conditions other than CH which in the opinion of the clinician may interfere with the study
- Serious drug habituation and/or overuse of acute headache medication (use on 10 or more days per month) for other headaches than CH
- Inability to complete the (electronic) diary in a sensible and accurate manner
- Structural intracranial or cervical vascular lesions that may potentially cause CH
- Previous destructive surgery involving the C2 or C3 roots (vertebrae) or deep brain stimulation
- Enrolment in other clinical studies that may confound the results of this study
- Requiring anticoagulation therapy or antithrombotic or thrombocyte aggregation-inhibitor for a concomitant condition that cannot be stopped peri-operatively. The local peri-operative protocol of each individual participating centre will be followed

9. Protocol Description

9.1 Detailed research plan

When a patient meets all eligibility criteria, the neurologist from the participating centre will discuss the case with the study coordinator and/or refer to a study neurologist. There will also be a consultation of the study implanter. When it is decided that the patient can be included for the study, there will be an informed consent first. It will approximately take two months to schedule the surgery. The patient will undergo the pre-operative screening and will fill in a daily (electronic) diary for four weeks to practice first, followed by eight weeks before surgery. Randomisation will take place if the patient still fulfils eligibility criteria after completing the pre-operative headache diary for 12 weeks. The surgery will be planned in advance because of potential waiting lists.

Pre-operative evaluation

- Written informed consent
- Common internal and neurological examination
- Pre-operative consultation of an anaesthesiologist
- MRI must be available (not older than 4 years) or performed and must be repeated after any changes in symptoms to exclude an underlying cause of the CCH. MRA of head and neck may be performed according to study physician's individual judgement.

Questionnaire **(in ProMISe):**

- medical history, medication use now and in the past, course of the disease (PCCH or SCCH), social habits: smoking, alcohol, coffee, previous response to medication: intolerability or no or little response)

Electronic headache diary for 12 weeks (of which 4 are to practice) **(in ProMISe):**

- Each attack of CH
- Pain intensity (0-10) during the last 6 weeks of baseline and each treatment period (of which the first 2 are for practice)
- Number of attacks per day of CH and other forms of headache

- Use of prophylactic or acute medication
- Monthly SF-36 questionnaire

Interview by telephone:

- A questionnaire about health consumption and absenteeism from work

The operating neurosurgeons or anaesthesiologists will use a uniform technique, described in section 10.2 in this protocol.

9.2 Schedule

Visit 1: study neurologist: inclusion/exclusion criteria

Visit 2: visit neurosurgeon (or implanter)/investigator: information about the surgery and study: reflection period of 7-14 days (or as long the patients needs)

Visit 3: informed consent study neurologist. Start electronic diary

Visit 4: anaesthesiologist

Evaluation headache diary by study coordinator: does the patient still meet inclusion criteria: at least 4 attacks per week?

Interview by telephone (medical student): economic evaluation questionnaire

Randomisation

Visit 5: surgery and defining stimulation parameters: 2-3 days in hospital

Visit 6: **+10 days** control of wound and removal of stitches **t=0** and calibration of stimulation

Visit 7: + 1 month: checking and changing of stimulation follow-up

Visit 8: + 2 months checking and changing of stimulation follow-up

Visit 9: + 4 months: checking of stimulation follow-up

Interview by telephone (student) after 6 months: economic evaluation questionnaire

Visit 10: + 6 months: checking of stimulation follow-up

Plus monthly visits study neurologist (an exception will be made for the visits at 3 and 5 months follow-up, because in case the participating patient prefers a telephone call instead, this will be allowed)

Open trial:

Visit 11: + 9 months: checking of stimulation follow-up

Visit 12: + 12 months: checking of stimulation follow-up

Plus three-monthly visit study neurologist

9.3 Interview by telephone

The patient will be interviewed by telephone twice by a medical student to answer a questionnaire about health consumption and absenteeism.

9.4 Data

The study coordinator is involved in coordination, collecting and analysing data.

9.5 Stimulation parameters

Setting stimulation parameters will be done by one of the case-managers (specialized nurses), the neurosurgeon or the anaesthesiologist who implanted the device (not blinded).

9.6 Surgery and hospital visits

The period of surgery and defining and adjusting the stimulation parameters will take approximately 2-3 days. After 10 days, the patient returns to the hospital for examination of the wound and removing stitches and test the system (impedances), and calibration of stimulation. After month 1, 2, 4 and 6 the patient will return to the clinic for evaluation and stimulation adjustments. The study neurologist will be seeing the patient on a monthly basis during the blinded part of the study(with the exceptions of visits 3 and 5 months follow-up which can be replaced by telephone calls in case the patient prefers this); this will be on a 3-monthly basis during the second part. During these evaluations the following scores will be taken (in the electronic diary or during an interview): *for details see appendix 24.1*

Electronic diary in Promise:

- Medication use
- Frequency of attacks of CH and other headache attacks
- Intensity of attacks: Numeric pain rating scale (only during the 6th and 12th month and 2 weeks before for practice)
- Absenteeism from work
- The awareness of paraesthesias: localisation (coding system) and strength (0= no paraesthesias 10= strongest paraesthesias
- Monthly SF-36

Interview:

- Adverse events; painful stimulation, neck stiffness, uncomfortable feeling of the device, infection, lost sensation of stimulation, when suspected lead migration: X-ray cervical spine
- Patient satisfaction

Before evaluations patients fill in their daily electronic diary, which will be send to our database after every 7 days (the patients will get a reminder per email or telephone). In the case of holiday, or not possessing a computer with internet access or another reason that discourages the patients from filling in the electronic diary, the patient receives a hard copy form of the diary, which can be copied to the electronic diary later.

At 6 and 12 months post randomisation, all patients return to the study neurologist/ study coordinator for the final recording of the headache diary and interview. The patient will be asked at 6 and 12 months follow-up to which group they think they have been randomised in the first 6 months treatment period and if he/she would recommend the treatment to other patients.

After ending the study, the study patients will be able to continue the study treatment on compassionate grounds. This will mean that they will continue to receive treatment at the study centre as is necessary for the ONS.

10. Methods

10.1 Defining stimulation amplitudes

The amplitude of stimulation will be established for each individual patient by determining the patient's individual therapeutic range as described in Trentman et al. (26). They found a mean amplitude for perception of 1.07 V and discomfort of 3.63 V. Stimulation frequency and pulse width will be uniformly held constant at 60 Hz and pulse width at 450 μs. The perception and discomfort amplitude will be defined by increasing the stimulation amplitude in steps of 0.1 V. The head will be in neutral position. The amplitude at which the patient starts feeling paraesthesias is called the perception threshold. The threshold at which the patient does not want the voltage to be increased any further because of painful sensations is designated the discomfort threshold. 100% stimulation is defined as stimulation at 90% of the range between perception and discomfort thresholds. Consequently, 30% stimulation means a stimulation level at 30% of the range between perception threshold and 100% stimulation level. The same goes for the 10%, 20%, 40% and 70% stimulation. Defining these thresholds will be done using a standard method by trained nurses or doctors and will be repeated 3 times, and only accepted if the values differ no more than 20%. The procedure will be repeated until the values differ no more than 20%.

Definitions:
DT: Discomfort threshold
PT: Perception Threshold
$SL_{100\%}$ stimulation: 100% stimulation level

Formula:
$SL_{100\%} = PT + 0.9 \times (DT-PT)$

$SL_{X\%} = PT + (SL_{100\%} - PT) \times X/100$

Example: PT: 1.0 V and DT: 6.0 V.

$SL_{100\%} = 1.0 + 0.9 \times (6.0-1.0) = 5.5V.$

$SL_{20\%}$ = 1.0 + (5.5-1.0) x 20/100 = 1.9 V

$SL_{70\%}$ = 1.0 + (5.5 – 1.0) x 70/100 = 3.3 V

10.2 Surgery

Since there will be no trial stimulation, the proposed abdominal location of the Implantable Pulse Generator (IPG) should be discussed with the patient on beforehand. In case of contra indications according to the patient or implanter for placement of the IPG abdominal, another location will be chosen for instance on the buttock. The procedure is performed under general anaesthesia and antibiotic prophylaxis: Cephalozin 1 or 2 g (according to local guidelines) (when the patient is allergic to certain antibiotics, please consult the hospital microbiologist for advice) given half an hour prior to actual surgery. The procedure will be done in two tempi. **First** the patient is positioned in a prone position with his/her head facing downwards in an adjustable U shaped headrest. After removing hair from the upper neck/lower occipital area using a clipper and disinfecting twice the area from low occipital to the left flank, an incision drape is used when sterile draping is applied to the surgical site. Using fluoroscopy the skin is marked at the level of vertebral arc C1. Here, a small area is infiltrated with a mixture of Lidocain(10mg/ml) /Epinephrine(5mcg/ml), before a small (2 cm) cranio-caudal incision is made. A 2-3 cm diameter subcutaneous pocket is prepared. The Touhy needle is slightly bent and then under fluoroscopic guidance inserted in lateral direction just beneath the skin and outside the fascia. The Quad Plus® (56 cm length; or shorter according to the length of the patient and preference of the implanter) is inserted after the stylet is removed. It is advanced until all electrodes are covered, then the Touhy needle is removed whilst keeping the lead in place. The lead is secured with a Titan anchor® that is fixed to the midline-fascia in the pocket with nonresorbable sutures (Mersilene® 1-0). By slightly pulling the lead the fixation is checked.

On the contralateral side, exactly the same procedure is performed. With the lead passer the lead is then subcutaneously led to the left flank, an in-between incision may

be required. The lead is looped at least two sites along the way, to avoid inadvertent damage by possible traction. Finally all wounds are sutured.

In a **second period** the patient is positioned laterally, right side facing down. The surgical area (flank towards left abdomen or buttock where the agreed upon spot is marked for the IPG) is disinfected twice and sterile (incision) drapes applied. A 7-8 cm paraumbilical incision is made at the marked site, a pocket (5x5 cm) is made using blunt dissection (no monopolar cautery allowed) in the subcutaneous fat layer over the abdominal fascia. The incision in the flank is re-opened and a small pocket (3x3 cm) is made there as well. From here the passer is inserted to the abdominal pocket. The lead extensions are pulled through and connected to the leads. The connection is covered by a silicon sheet fixed with nonresorbable sutures. The extension cables are connected to the IPG (Versitrel™) which is implanted into the pocket and secured with 1 or 2 nonresorbable sutures. The N'vision™ programmer is used to analyse impedances of this neuromodulation system. When there are no system failures, remaining wounds are sutured.
SUMMARY: Low occipital bilateral Quad Plus, midline to laterally directed, secured by titan anchors, connected to Versitrel. No trial stimulation. Suggested stimulation parameters: Pulse width: 450, Amplitude: protocol, Rate: 60.

10.3 Devices used

IMPLANTABLES (Medtronic order nr)if a Versitrel IOG is used: IPG: Versitrel™ (7427V), Extension cable: Low profile Quad extension cable 10-60 cm, length depends on patient characteristics (7489 10-60), Lead: Pisces Quad® Plus 56 cm (388856) (or a different length), Fixation: Titan Anchor® (3550-39), Versitrel™ Patient Programmer (7435)
It is also allowed to use the Prime Advanced IPG (37702) with compatible extension cables in stead of the Versitrel IPG, as this IPG the 'newer version' of the Versitrel (7427V) and some implantation sites are more common with this. The most important difference is the more advanced software, which will only matter to the nurse or doctor adjusting the stimulator, because it is easier in use. We don't think the participating patients will be caused disadvantage by using either IPG.

IMPLANTABLES (Medtronic order nr) if a Prime Advanced IPG is used: Prime Advanced™ (37702), Bifurcated extension cable 20-40-60 cm, length depends on patient characteristics (37082-20/ -40/ -60), Anchor injex bumpy or injex bi-wing (97791 or 97792), Plug (3550-29), 2 Quad-plus electrode 28-33-45-56 cm, length depends on patient characteristics (3888-28/ -33/ -45/ -56), Trialling cable (3555-31), Mystim (97740).

11. Economic evaluation

The objective of the economic evaluation part of this study is to examine whether the delivery of high (100%) stimulation compared to low (30%) stimulation is preferable in terms of costs, effects and utilities from a societal perspective.

11.1 Design and participants

Economic evaluations compare additional costs and additional outcomes of high stimulation compared to low stimulation. This economic evaluation will involve a combination of a cost-effectiveness analysis (CEA) and a cost-utility analysis (CUA). In a CEA effects are presented in clinical outcomes (in our study frequency of CH attacks during the last 4 weeks of the 100% stimulation period and the 30% stimulation period). The primary outcome measure for the cost-utility analysis will be Quality Adjusted Life Years (QALYs), based on the SF-36 utility scores (29-31). In the CUA, the Incremental cost-effectiveness ratio (ICER) will be expressed as the incremental costs per QALY. This economic evaluation will be performed from a societal perspective, which implies that all relevant costs and outcomes will be taken into account. With regard to this research question we hypothesize that the high stimulation is associated with an increased effect, and an increase in quality of life. The time horizon will be the same period as the follow-up period of the double blind part of the main study, 6 months. Costs (the use of resources) will be measured continuously using a (retrospective) questionnaire (6 months); outcomes for the economic evaluation study will be measured at pre-test before random assignment into groups (baseline), and at 6 months.

The second part of this economic evaluation will be a cost-of-illness (COI) study. The objective of this COI analysis is to calculate the societal costs of MICCH in the Netherlands. This prevalence based, retrospectively and bottom-up cost of illness

study will be performed at baseline using a (retrospective) questionnaire (6 months) and an electronic diary for the use of attack medication.

11.2 Measurement

Cost measures

Total costs will be estimated using a bottom-up (or micro-costing) approach, where information on each element of service used is multiplied by an appropriate unit cost and summed to provide an overall total cost (32). We will assess intervention costs, healthcare costs, patient and family costs, and costs outside the health care sector. For this study we developed a cost questionnaire especially designed for this group, based on existing questionnaires, which will identify all relevant costs aspects (33;34).

To measure the actual use of resources data will be obtained using combined sources (registrations by professionals and cost questionnaire). Resources used relating to the interventions will be based on the registered time all professionals spent on the treatment. Intervention costs will include all the costs that will contribute to the procedure of ONS. All use of resources by the patient and their family in and outside the health care sector, will be measured by means of an interview by telephone, in which they are being asked about volumes of resource utilization 6 months retrospectively at baseline and at 6 months follow up. Cluster headache medication use will be registered in the electronic diary. These 2 sources of information will be combined.

The valuation of healthcare costs, patient and family costs will be based on the updated Dutch manual for cost analysis in healthcare research (35;36). This manual recommends using standardized cost prices. In brief, the manual recommends that prices of informal care will be based on shadow prices for unpaid work (meaning a standard cost price based on general hourly wages). Costs of medication will be calculated using prices taken from the Dutch Pharmacotherapeutic Compass (37). Productivity costs will be calculated by means of the friction cost method, based on a mean added value of the Dutch working population. The friction costs method takes into account production losses confined to the period needed (usually 90 days) to replace a sick employee. In case of uncertainty we will use a conservative estimation

(i.e. the lowest cost price). Cost prices will be expressed in 2009 euro's. If necessary, existing cost-prices will be updated to 2011 using the consumer price index (CPI) (35;36).

Outcome measures

The primary outcome measure for the cost-effectiveness analysis will be increase in health status as measured by the CH attacks 4-weekly at 6 months of follow-up of the last month of both treatment arms. Within the cost-utility analysis, utilities will be derived using an indirect preference-based technique. In this technique, the patient's health status will be monthly measured by means of the standard Dutch version of SF-36 and weights, that incorporate preferences from a general population sample, will be used to calculate utilities from the SF-36; the Short Form 6D (SF-6D) (29;31). The SF-36 will be completed monthly in the electronic diary and the cost questionnaire will be completed at baseline and at 6 months follow-up by an interview by telephone. The SF-36 is chosen because it is a widely used quality of life instrument (nationally and internationally), also in the field of headache (38). Utility values can be calculated for these health states, using preferences elicited from a general population, the so-called Brazier algorithm (29). The utility values derived from the Brazier algorithm will be used to compute QALYs. The Brazier algorithm has been established using a general population from the UK (29). The utilities at the time points will be used to compute a QALY score by means of the area under the curve method.

11.3 Analysis

No power calculations will be performed for the economic evaluation study as it is embedded in an RCT. Our primary (base-case analyses) will be performed according to the intention-to-treat principle, including data from all participants regardless of whether they received the intervention or not. For the analyses we will use SPSS statistical software and Excel database (for the Bootstraps).

To investigate whether data are normally distributed a Kolmogorov-Smirnov test will be performed. Despite the usual skewness in the distribution of costs, the arithmetic means will be generally considered the most appropriate measures to describe cost

data (39;40). Therefore arithmetic means (and standard deviations) will be presented. In case of skewness of the cost data, non-parametric bootstrapping will be used to test for statistical differences in costs between the 100% stimulation and the 30% stimulation group. Non-parametric bootstrapping is a method based on random sampling with replacement based on individual data of the participants (41). The bootstrap replications will be used to calculate 95% confidence intervals around the costs (95% CI), based on the 2.5th and 97.5th percentiles. If cost data are distributed normally, t-tests will be used.

The ICER will be determined on the basis of incremental costs and effects of high stimulation compared to low stimulation. The cost-effectiveness ratio will be stated in terms of costs per outcome rate, the cost-utility ratio will focus on the net cost per QALY gained. The ICER will be calculated as follows. ICER = (Ci – Cc) / (Ei – Ec), where Ci is the annual total cost of the high stimulation group, Cc is the annual total cost of the low stimulation group, Ei is the effect at one year follow-up for the high stimulation group and Ec is the effect at one year follow-up for the low stimulation group. The robustness of the ICER will be checked by non-parametric bootstrapping (1000 times). Bootstrap simulations will also be conducted in order to quantify the uncertainty around the ICER, yielding information about the joint distribution of cost and effect differences. The bootstrapped cost-effectiveness ratios will be subsequently plotted in a cost-effectiveness plane, in which the vertical line reflects the difference in costs and the horizontal line reflects the difference in effectiveness. The choice of treatment depends on the maximum amount of money that society is prepared to pay for a gain in effectiveness, which is called the ceiling ratio. Therefore, the bootstrapped ICERs will also be depicted in a cost-effectiveness acceptability curve showing the probability that high stimulation is cost-effective using a range of ceiling ratios.
Additionally, to demonstrate the robustness of our base-case findings a multi-way sensitivity analyses will be performed. In the sensitivity analysis uncertain factors of assumptions in the base case analysis will recalculated in order to assess whether the assumptions have influenced the incremental cost-effectiveness ratio (ICER), for example by varying cost-prices and volumes between minimum and maximum (41).

11.4 Cost-of-illness (COI)

The objective of this COI analysis is to calculate the societal costs of MICCH in the Netherlands. This prevalence based, retrospectively and bottom-up cost of illness study will be performed at baseline. Data for this COI will come from the baseline measurements of the a cost questionnaire especially designed for this group, based on existing questionnaires, which will identify all relevant costs aspects (33;34). The valuation of the COI will be based on the same methods as used in the economic evaluation (37).

12. Protocol deviations

Investigators are required to adhere to the Investigational Plan, signed Investigator's Agreement, applicable national or local, laws and regulations, and any conditions required by the appropriate Ethics Committees (EC) or applicable regulatory authorities.

Deviations from the protocol will not be permitted, except where necessary to protect the life or physical well-being of a patient in an emergency situation. If circumstances permit, the investigator should inform study management before initiating deviations. Prior notification is generally not expected in situations where unforeseen circumstances are beyond the investigator's control (e.g. patient did not attend scheduled follow-up visit). The investigator is required to adhere to the EC procedures for reporting deviations. Deviations include, but are not limited to the following:

- Failure to obtain informed consent prior to patient enrolment
- Incorrect version of the informed consent form used
- Enrolled patient did not meet the inclusion/exclusion criteria
- Adverse Events not reported by investigators in the required timeframe as specified in the protocol

Centre compliance with regard to deviations will be reviewed by the study coordinator on a timely basis. In addition, all deviations from the CIP will be documented in the final report.

13. Safety monitoring

The study investigators are responsible for the detection and documentation of adverse events (AEs) and device events.

13.1 Adverse Event Definitions

Definition/classification

For the purposes of the clinical report, each adverse event will be classified according to EN ISO 14155-1.

Where the definition indicates "device", it refers to any device used in the study. This might be the device under investigation, or any market released component of the system.

13.2 Adverse Event (AE):

Any untoward medical occurrence in a subject.

NOTE 1: This definition does not imply that there is a relationship between the adverse event and the device under investigation.

13.3 Adverse Device Effect (ADE):

Any untoward and unintended response to a medical device.

NOTE 1: This definition includes any event resulting from insufficiencies or inadequacies in the instructions for use or the deployment of the device.

NOTE 2: This definition includes any event that is a result of a user error.

NOTE 3: This definition includes patients and users.

13.4 Serious Adverse Event (SAE):

An adverse event that

a) led to death

b) led to a serious deterioration in the health of a subject that

1) resulted in a life-threatening illness or injury,

2) resulted in a permanent impairment of a body structure or a body function,

3) required in-patient hospitalization (except for the implantation) or prolongation of existing hospitalization, or

4) resulted in medical or surgical intervention to prevent permanent impairment to body structure or a body function

c) led to fetal distress, fetal death or a congenital abnormality or birth defect.

Explanatory note: an Adverse Event is considered Serious if condition 1, 2, 3, or 4 apply in combination with a serious deterioration in health. E.g. a planned hospitalization for a pre-existing condition, without a serious deterioration in health is not considered to be a SAE.

13.5 Serious Adverse Device Effect (SADE):

An ADE that has resulted in any of the consequences characteristic of a Serious Adverse Event or that might have led to any of these consequences if suitable action had not been taken or intervention had not been made or if circumstances had been less opportune. *NOTE:* the definition of SADE includes incidents and near incidents.

13.6 Recording and reporting of AEs and device events

Adverse Event (AE) information will be collected throughout the study and reported to the study coordinator on an Adverse Event Form. This Adverse Event form should be sent to the study coordinator. Contact details are given on page 1. All Adverse Events, regardless of relatedness or outcome, must be reported.

Information reported on the Adverse Event Form shall include a description of the event, the date of event onset, the relatedness of the event to the procedure, the relatedness of the event to the device, actions taken as a result of the event, the outcome of the event, and the date the event was first noticed by the investigator.

For Adverse Events that require immediate reporting (see table 1), initial reporting may be done by e-mail, or on the CRF completed as much as information is available, followed by the completed original adverse event form.

All other AE's must be reported in a timely manner.

13.7 Adverse Event review process

All adverse events will be reviewed by the study coordinator. This review will include the determination whether the adverse event meets regulatory reporting requirements.

Table 1*:* Adverse Event reporting requirements	
Serious Adverse Device Effects (SADE)	
Investigator submit to:	
PI/study coordinator	Immediately after the investigator first learns of the event.
MEC	Reporting timeframe as per local MEC requirement.
PI submit to:	
Regulatory Authorities	Reporting timeframe as per local requirement.
MEC	Submit to MEC per local reporting requirement.

13.8 Outcome

The outcome of the AE should be classified according to the following definitions:

- Ongoing: the event is ongoing and has not yet resolved.
- Recovered / resolved: the event has resolved without sequelae (no further symptoms are present and no treatment is being received by the patient).
- Recovered / resolved with sequelae: the event has resolved but there may be lingering effects present (e.g., a scar following a cut or abrasion).
- Fatal: the patient died as a result of the event. This code should only be used for the event that caused the death, not any event that was present at the time of the patient's death. Fatal events require immediately reporting to the sponsor (or an authorized representative).
- Unknown: may only be used in the event that the patient is lost to follow-up and no reliable data can be obtained.

All efforts should be made to classify the AE according to the above categories.

13.9 Follow-up of Adverse Events

All AEs occurring during the study are to be followed up in accordance with good medical practice until resolved or judged no longer clinically significant, or if a chronic condition, until fully characterized. All follow-up results are to be reported in the eCRF. Assessment should be made at each visit (or more frequently, if necessary) of any changes in severity, the suspected relationship to the device, the interventions required to treat it, and the outcome.

13.10 Patient Death

All patient deaths during the investigation should be reported to the principal investigator within 24 hours.

Notification of death should include a detailed statement of the pertinent events and be signed by the investigator or authorized personnel in addition to the appropriate CRF(s) ("Patient Death" and "Adverse Event" forms where applicable). It is the investigator's responsibility to notify the appropriate Ethics Committees (EC). Details of death should be included in a letter to the principal investigator summarizing the patient's course since enrolment in the study and the following information (Patient's anonymity will be protected on all documents provided):

- Date and time of death;
- Place death occurred (e.g. hospital, nursing home, patient's home);
- Whether death was witnessed;
- Cause of death (if known);
- Any other circumstances surrounding the death;
- Approximate time interval to death from the initiating event;
- Whether it was device or procedure related;
- Device configuration at time of death;
- Autopsy report (if performed).

If available, also provide clinical notes and witness statements. All appropriate case report forms must be completed.

14. Study Termination

If a patient wishes to withdraw from the study at any time, he/she would be able to do so without having to justify it and without affecting his/her relationship with the investigator. Also, an investigator may withdraw a patient from the study at any time if he/she thinks it is in the patient's best interest. In either case, the investigator will be requested to complete a "Termination Form" for any patient that leaves the study for whatever reason.

15. Administrative Procedures

15.1 Regulatory and ethical considerations

This study will be conducted according compliance with the Declaration of Helsinki and national law.

15.2 Informed Consent

Before a patient can participate in the study, the patient must give written informed consent (witnessed, where required by law or regulation). The informed consent process will be in accordance with ISO 14155, the Declaration of Helsinki, the European Data Protection Directive and local regulatory requirements. Patient informed consent (PIC) forms will be based on a master document (see Appendix 24.2), and must be submitted to the EC. Each potentially eligible patient will be informed of the study's objectives and overall requirements. Prior to conducting any study-specific procedures, the investigator will explain the study fully to the patient. Patients will be informed that they take part in a study comparing different conditions of stimulation. If the patient is willing to participate in the study, he/she will be requested to give written informed consent after being given sufficient time to consider his/her participation and the opportunity to ask for further details. The PIC

will be signed and personally dated by both the patient and the investigator. A copy of the signed form will be provided to the patient, and the original will be retained with the source documents.

15.3 Ethics Committee Requirements

Before initiation of the study at a given site, approval of the protocol, PIC, and any information presented to potential patients must be obtained, in accordance with the declaration of Helsinki, from the appropriate EC. A signed and dated statement that the protocol and informed consent have been approved by the EC must be given to the coordinating clinical investigator before study initiation. This approval must include the protocol and informed consent versions numbers to ensure use of the approved study documents. If any amendments to any of these documents occur during the study, approval must be obtained prior to their implementation. The investigator is responsible for ensuring that these actions occur. The EC is required to keep the sponsor application for at least 3 years after the completion of the study.

15.4 End of the Study

For administrative and safety reporting purposes, the end of the study will be defined as the last visit of the last patient. This provides for a single and conservative definition across all study sites.

15.5 Patient confidentiality

The investigator must ensure that the patient's anonymity is maintained. All data and measurements on participants in this trial will be entered via and managed by a secure data management application, ProMISe, of the department of Medical Statistics & BioInformatics of the LUMC. Data are accessible only via secure internet connections, using the Internet Explorer browser and access is limited to explicitly authorized users each of whom has his or her personal username and password. All access to the system is fully audited and logged and all changes can be traced back to their origin. The ProMISe system also performs routine quality checking and error reporting. The study coordinator has full access to the system. The randomisation

table is however fully shielded from all personnel except the trial statisticians and implanter/ case manager. ProMISe is a generic clinical data management system and extensively tested through its application in over 100 clinical registries and trials in Europe. Documents not for submission, such as signed PICs, should be maintained in strict confidence by the investigator. The sponsor will ensure that no patient will be identifiable either from the final report or published results.

16. Statistical methods

16.1 The aim of the study

[1] to prove that the treatment has a beneficial effect over follow-up time since start of treatment
[2] after [1] has been established, to prove that there is a dose-response effect.

While (1) may be ascribed (at least in part) to a placebo effect, we believe that (2) cannot, since its associated effect measure is based on a between group comparison with random allocation to which the patient should be sufficiently blinded.

16.2 Endpoints

The primary endpoint is the mean attack frequency (MAF). Let MAF0 and MAF6 denote the MAF at baseline and the MAF at six months for a given patient. MAF0 is the baseline value for each individual patient of the primary endpoint and hence will be taken into account in the analyses as a covariate; although the primary comparison is a randomised one and MAF0 strictly speaking does not need to be taken into account, incorporating this value into the analyses will increase power and allows secondary analyses with respect to possible interaction between the treatment and the baseline level.

The MAF has a skewed distribution, and therefore we will take the (natural) logarithm in our analyses. If case MAF6 is equal to zero, we will add the minimal possible value of 0.25 (corresponding to a single attack per month) to allow taking the logarithm.

The analyses will take the general shape of a regression analysis with lnMAF6 as the dependent variable, lnMAF0 as the covariate and treatment as a fixed factor. An interaction between treatment and lnMAF0 will be added in a secondary analysis.

We assume the following model: lnMAF6= a +b*lnMAF0 + c*Treat, where Treat=0 for 30% stimulation and Treat=1 for 100% stimulation, thus being an indicator variable for the randomly allocated arm.

First we use an F test to evaluate (at the 5% level) the null-hypothesis

(1) $H_0$1: a=0 & b=1 & c=0

(effectively comparing this model to the null-model: lnMAF6=lnMAF0 in both randomised groups)

Rejection of this null-hypothesis means that we have confirmed a stimulation effect over time. Now, ONLY if (1) is rejected, do we test the following three null-hypotheses

(2a) $H_0$2a: a=0 & b=1 conditional on Treat=0 (30% stimulation)
(2b) $H_0$2b: a=0 & b=1 conditional on Treat=1 (100% stimulation)
(2c) $H_0$2c: c=0 (no stimulation intensity effect)

Rejection of (2c) means that we have confirmed a dose-response effect, in other words a difference between 30% and 100% stimulation.

16.3 Multi testing correction

We claim that upon rejection of (1), we may simultaneously test (2a), (2b) and (2c) at the 5% level, while maintaining the probability of falsely rejecting a single null hypothesis at 5% (so without the need for correction for multiple testing). This follows from the so-called closed testing principle (42). The underlying idea is that if null hypothesis (1) is false, then *at most one* of (2a), (2b) and (2c) can be true. The

closed-testing principle has been applied before in clinical trials but not very often (43). The method is more powerful than the more familiar "gate keeping" procedure, where we test hypotheses (1), (2c), (2b) and (2a) in order, and stop as soon as we fail to reject one.

The issue of multiple testing in biomedical research in general and in clinical trials in particular, is discussed by Bender and Lange (44).

16.4 Power and sample size

Because of limited information about the distribution of the MAF for our specific group of patients, we conducted a small pilot study. We found a MAF of 26.42 attacks per week, with a standard deviation of 15.38. These findings did not differ very much from figures given by Burns et al. (7). These numbers correspond to lnMAF having a a mean of 3.13 and a standard deviation of 0.54.

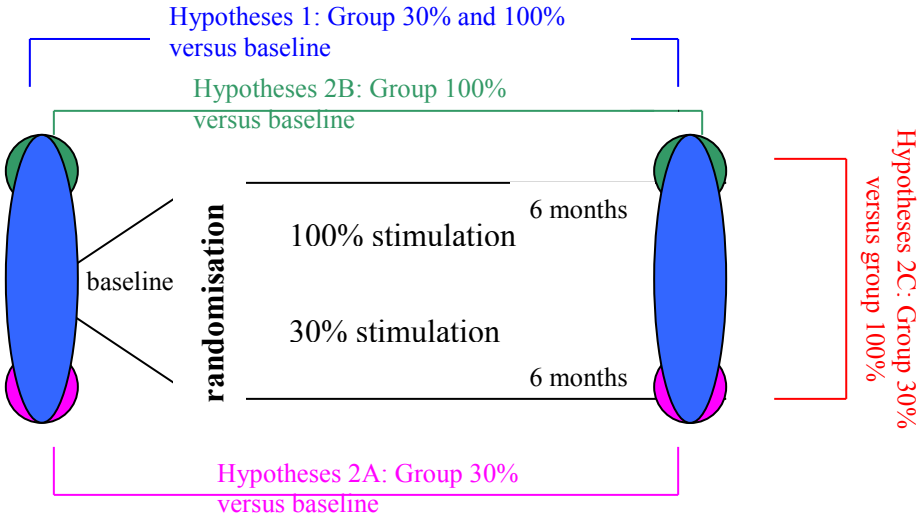
We expect (MAF6 – MAF0) to be -9 on average in the 100% stimulation group, while we expect no reduction in the 30% stimulation group. This corresponds to (lnMAF6 – lnMAF0) being -0.42 on average in the 100% stimulation group.

If we assume that lnMAF0 and lnMAF6 are positively correlated, then the standard deviation of Delta = (lnMAF6-lnMAF0) would be in the range from 0.54 to $\sqrt{2}$ *0.54=0.76. Powering in terms of this Delta is a fair approximation to the regression analysis model; in fact, if the coefficient b would be equal to 1, the calculations would be identical.

Note that tests (1), (2a) and (2b) are in essence paired tests, comparing for each patient a change with respect to baseline. Test (2c) is an independent, two sample test because we compare the two treatment arms. Consequently, the test for (2c) will be the least powerful and so we performed our power analysis for that test. We did verify that all other tests are more powerful.

We attach the results of our power analysis. We conclude that if the standard deviation is 0.54and the average of (lnMAF6-lnMAF0) is about -0.42, then 60

patients in each arm will allow us to detect the difference with probability 98%. Taking a possible 20% drop-out rate into account, we propose a total study size of 144 divided equally between both arms.



16.5 Analyses

We will use an intention to treat approach in all our primary analyses. A per protocol analysis will be undertaken if substantial deviations from the allocated treatment or a substantial amount of missing values are observed. In all cases the per protocol analyses will serve as a "sensitivity analysis" as intended by the ICH9 guidelines and a further support for proper interpretation of the ITT conclusions.

Patients switching to steroids will be withdrawn from further data collection but are retained in the study as such. Their MAF will be included up to the time they started the new medication.

Apart from the primary analyses which focus on a specific time point (6 months), secondary analyses will take the full repeated measurements structure into account, including the 6 months values. We use a mixed model for repeated measurements with time since randomisation as a fixed covariate (or factor), lnMAF0 as a

continuous covariate and Treat as a fixed factor. We will apply an AR1 covariance structure unless the data prove this to be untenable. This model is a direct extension of the simple regression model used to test the primary hypotheses and allows estimation of treatment effect over time, including possible interactions. We will also analyze the data using generalized estimating equations (GEE), aiming to consolidate the results from the mixed model analysis.

The mixed model will take the missing values into account in a natural way, assuming of course missingness at random. A sensitivity analysis will be undertaken to verify this assumption.

16.6 Randomisation and blinding

Patients are randomised using a variable blocked stratified balanced design. The entire randomisation is generated before the first patient enters the trial and fixed. The randomisation table, although stored with the trial data base, is not accessible by users of the data management system except for the trial statistician and the implanter and casemanager. When a patient is entered into the (web based) data management system, the eligibility criteria are checked and the required stratification variables are specified. A request for randomisation is generated by the system and the next available record with the correct stratification values in the hidden randomisation table is allocated to the patient; both patient and randomisation record have a unique key which is stored both in the data tables and in the randomisation table.
In the clinical data base the fact that the patient has been randomised, is made known by storing a random key which points to the record in the randomisation table. However, the web based interface does not allow any data manager or clinician to see the randomisation result if not authorized so by the very design of the trial.
When the study data have to be analyzed according to randomised treatment, the randomisation table can be extracted from the data base by the statistician and joined to the clinical data extracted by the data manager of the trial.
In case of emergency the statistician or implanter can either log on to the system and retrieve the randomisation of a patient via his (authorized) account or the randomisation table can be viewed directly in case the internet connections break down (but only from within the dep. of Medical Statistics). A backup of the

randomisation table is by definition assured since the entire data base is back up every day.

17. Risk assessment

ONS most important, known, related risks include: lead migration , low battery, neck stiffness (45). The risk of lead migration is probably related to the surgery technique used. In a recent Dutch study in 4 patients treated with ONS, there was no lead migration (unpublished data) or any other complications after 1.5 year follow-up. Other possible complications are unpleasant sensations of paraesthesias, haematoma, limited neck movements, skin discomfort, hardware failure (e.g. early end of life of the battery, which can cause sudden increase of headache) and infection.

Treatment-as-usual related risks are related to the medication used and do not increase due to participation in this study.

Until now, no persistent iatrogenic neurological deficit has been reported using ONS.

Low Battery

A low battery has to be surgically replaced. This will eventually occur in all patients, so it can be debated if an empty battery must be considered as a complication.

18. Investigator / Site Selection

18.1 Implantation site

Site selection for implantation will be based on experience with and interest in ONS therapy for headache. Sites will be located in The Netherlands, UK and Denmark and probably Germany and Belgium.

In order to qualify for participation in the study, sites are required to meet the following criteria:

1. Willing to comply with the Clinical Investigation Plan (CIP), all required procedures, the Declaration of Helsinki and local regulations
2. Expertise in chronic pain treatment with ONS therapy and programming the stimulator
3. Availability of physician programmer (N'Vision) to adapt the ONS programming parameters

18.2 Patient recruitment site

Site selection for recruitment will be based on experience with treating CCH. Sites will be located in Europe. The investigator must have sufficient time to address the study requirements, reporting requirements and must have experience in patient selection and management. There must be a patient recruitment potential of at least 4 - 8 CCH patients/year for the trial.

18.3 Training requirements

The following will be addressed prior to site activation and throughout the study as needed:

- Protocol specific training
- Study training relevant and pertinent to the involvement of personnel conducting study activities, including investigator responsibilities
- Product-specific information/device training
- Specifics of study conduct
- AE reporting

The site and sponsor will maintain documentation of attendance at each of these training opportunities.

19. Study Organization

Study Management

The study will be managed and coordinated by the Leiden University Medical Centre, Leiden, The Netherlands.

Study Investigators

19.1 Principal Investigator

Name	Prof. Michel D. Ferrari MD, PhD
Hospital	Leiden University Medical Centre
Department	Neurology
Address	PO Box 9600
City	2300 RC Leiden
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Tel:	+31-71-526-2895
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19.2 Coordinating Clinical Investigator

Name	Patty G.G. Doesborg, MD
Hospital	Leiden University Medical Centre
Department	Neurology
Address	PO Box 9600
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Country	The Netherlands
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19.3 Amendment Procedure

Any amendment to the Clinical Investigation Plan will be agreed by Coordinating Clinical Investigator and Principal Investigator prior to submission to Ethics Committee and Competent Authorities if applicable.

19.4 Boards

The Steering Committee will monitor the study and review its progress at regular intervals. Based on these reviews and Data Safety Monitoring Board (DSMB) outcomes, the Committee may request that the study be put on hold or even terminated for safety, ethical or other reasons.

An independent DSMB will be established prior to study enrolment and will have a minimum of three members with relevant expertise, and experience in clinical studies and/or as a DSMB member for another study. All members will lack significant conflicts of interest and one will be a biostatistician knowledgeable in the area of statistical methods used for clinical studies. One DSMB member with previous experience will be appointed as the chairperson.

A DSMB Charter (or Manual of Operations) will be developed and agreed upon by the Sponsor and all DSMB members prior to the review of study related data. The Charter will describe its functions including, but not limited to, the following:

- Meeting schedule and format
- How the confidentiality/blinding of the data will be maintained
- Who may attend all or part of the meetings
- How conflicts of interest for potential committee members will be assessed
- Timing and format for the presentation of data to the DSMB
- How recommendations will be communicated to the Sponsor
- Definition of a quorum
- Interim and final analysis
- Parameters for early termination
- Procedures for documenting meeting minutes
- Maintenance of relevant records

The DSMB will receive summaries of adverse events reports on a bi-annual basis. The board may meet after bi-annual review, if they believe it is necessary. However, the DSMB will be convened at least once a year, and additional meeting may be scheduled based on the accumulation rate of data on safety and effectiveness.

20. Ethical Basis

This study has been designed and shall be conducted according to the principles set in the Declaration of Helsinki 2008 revision and Good Clinical Practice (GCP)

Appropriate Ethics Committees approval for the study and the patient information sheet and consent form will be required prior to beginning the study. A copy of the approval is required by the LUMC prior to the first investigational product being implanted.

21. Insurance / Indemnification

Each participating centre maintains appropriate clinical trial liability insurance coverage as required under applicable laws and regulations and will comply with applicable local law and custom concerning specific insurance coverage. If required, a Clinical Trial insurance statement/certificate will be provided to the Ethics Committee for each individual participating recruitment or implantation centre. Indemnification statements will be provided as required per regulations.

22. Publication Policy

This study will be registered in a secured database in accordance with the Declaration of Helsinki, and data resulting from the study will be made publicly available. It is anticipated that at least one publication will be generated from the study results, to be published in a peer reviewed journal. The principle investigators will have access to all cleaned study data and can use it for scientific purposes. The investigators can propose projects to the principle investigators using the database.

With respect tot publication policy, the following aspects will be addressed:

1. All study results will be published without restrictions. This means that patients are entitled to the right that the study results will be published, based on their participation in the study.
2. All members of the study group agree that all study results will be published.
3. Both negative and positive results will be published.
4. Before publication, all authors will have the opportunity to give comments on the manuscript.
5. Data will be published as soon as possible after finishing data analysis.

Specific details will be described in a separate publication plan, which will be provided to investigators for review and agreement.

23. Study reimbursement

This study is funded by Medtronic with an unrestricted grant. The salary of the coordinating clinical investigator only is paid from this grant. Since 2013 Medtronic is willing to deliver the needed occipital nerve stimulation devices for the participants within the study, if this is not covered by their health insurance. After expiration or termination of the Research Agreement, Medtronic shall, pending approval through Medtronic's established internal process, provide replacement Devices until either: Medtronic no longer manufactures the Devices, the therapy/ devices (their components) has/have obtained Reimbursement or the ICON patient is no longer receiving benefit from the Devices, whichever occurs first. Medtronic has no influence on the study design, analysis or publication of the data. Dr. R. Buschman, department of Benelux and Nordic region, Medtronic, is a non-voting observing member of the Steering Committee.

24. Appendices

24.1

Case report forms

24.2

Informed consent

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