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# PARAGON

Patient Reported outcomes After Greater Occipital Nerve block

**The effect of patient positioning on patient reported outcomes after GON block for primary headache disorder; a multi-centre, four-arm, controlled, prospective randomised trial**

**Version 2, dd 23 Aug 2018**

Chief Investigator's Statement of Ownership and Content.

I, Dr Jitka Vanderpol, confirm that this protocol is my work and is owned by me. The protocol conforms with standards outlined in the Declaration of Helsinki 1964.

Name (PRINT): \_\_\_\_\_

Signature: \_\_\_\_\_

Date: \_\_\_\_\_

## RESEARCH PROTOCOL SUMMARY

<b>TITLE:</b>	The effect of patient positioning on patient reported outcomes after GON block for primary headache disorder; a multi-centre, four-arm, controlled, prospective randomised trial
<b>Short title:</b>	PARAGON; patient reported outcomes after GON block
<b>IRAS number</b>	248606
<b>Study type &amp; design</b>	A multi-centre, four-arm, controlled, prospective randomised trial of the effect of a patient's position during GON block intervention (ie non-medicinal, non-device)
<b>Patient population</b>	Adults with mental capacity and without any significant comorbidities who are diagnosed with a headache disorder (migraine [episodic or chronic], occipital neuralgia, cluster headache, trigeminal autonomic cephalgia [TAC], other) unresponsive or poorly responsive to pharmacological treatments.
<b>Primary objective</b>	Any difference in headache RELIEF score post-GON block intervention, as recorded by patients at 90 days post-intervention.
<b>Secondary objectives</b>	<p>Any difference in headache RELIEF score post-GON block intervention, as recorded by patients at 30 days post-intervention.</p> <p>Any difference in number of headache-free days post-GON block intervention (as recorded by patients using the Curelator headache app and retrospective recall) at 30 and 90 days post-GON block.</p> <p>Any change in headache severity, related symptoms, frequency and duration – baseline versus follow-up at 30 days and 90 days</p> <p>Impact of headache disorder on quality of life as measured by validated HIT6, MIDAS and MSQ questionnaires at 30 and 90 days</p> <p>Any change in prophylactic and/or rescue medication use, and its potential economic impact.</p> <p>Analysis of variables that may be associated with favourable outcomes after GON block through multi-regression analysis</p> <p>Safety of both patient positioning approaches post-GON block</p>

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<b>Research grant provider</b>	Curelator Inc
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<b>Organisation where research will take place</b>	<p>Cumbria Partnership NHS Foundation Trust Neurology Department, Penrith, CA11 8JA, UK</p> <p>City Hospitals NHS Sunderland Foundation Trust Neurology Department, Sunderland, SR4 7TP, UK</p> <p>Hull and East Yorkshire Hospitals NHS Trust, Hull Royal Infirmary, Anlaby Rd, Hull HU3 2JZ</p> <p>Newcastle upon Tyne Hospitals NHS Foundation Trust, Royal Victoria Infirmary, Newcastle, NE1 4LP, UK</p>

<b>Planned timeline</b>	Recruitment start date (first patient, first visit) Sep 2018, Recruitment end date (last patient, first visit): 30 June 2019 Recruitment end date (last patient, last visit): 30 Sep 2019
<b>Protocol version, date</b>	Version 2, dd 23 Aug 2018

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## **1. LAY SUMMARY**

Primary headache disorders, including migraine, cluster headache, and occipital neuralgia, are some of the most debilitating conditions that impact negatively on patients themselves and the wider economy. A subset of patients does not respond to currently available prophylaxis and rescue medication. Nerve block medication treatment is offered to these treatment-resistant patients. Greater occipital nerve block (GON block) is an established nerve block procedure that has a favourable safety profile and is cost-effective – the active ingredients used are a mix of local anaesthetic agent and steroid. The exact effectiveness and the optimal method for delivering GON block is to be finalised due to a relative lack of evidence from gold-standard randomised controlled trials and variety in the applied GON block procedure. Initial pilot data on GON block patients, and related evidence from use of anaesthetics in dentistry, suggests that lying a patient down for ten minutes after the procedure enhances the effectiveness of the GON block and thereby leads to an increase in the achieved headache-free period. This present study seeks to use a prospective, randomised, multi-centre approach to determine whether the patient's position straight after injection of the GON block medicine influences the patient-reported outcomes regarding headache symptoms afterwards. A headache-reporting App called Curelator, used by participating patients during the trial period, will allow prospective recording of headaches which may reduce the bias observed with retrospective patient recall of headache episodes.



## **2. INTRODUCTION**

### **2.1 Background Information**

Primary headache disorders including migraine, occipital neuralgia, and cluster headache have a high prevalence. In terms of years of life lost to disability, headache disorders rank third among worldwide causes of disability (Steiner et al, 2015). When considered separately, worldwide migraine has a one-year prevalence of over 10%, with a higher prevalence in developed countries (Robins and Lipton, 2010).

Oral pharmacological treatment of primary headache disorders is the mainstay of patient management, both in terms of prophylaxis and treatment of headache episodes. However, interventional procedures such as peripheral nerve blocks (PNBs) and trigger point injections (TPIs) have long been used in the treatment of various headache disorders (Evans and Yannakakis, 2001). Nerve blocks by means of Botulinum toxin type A or anaesthetic agents such as lidocaine or bupivacaine are established treatment modalities (Terzi et al, 2002; Levin, 2010; Escher et al, 2017). Although various nerves – such as lesser occipital, auriculotemporal, supratrochlear and supraorbital nerves, sphenopalatine ganglion, cervical spinal roots, and facet joints of the upper cervical spine - a common target is the greater occipital nerve (GON). There is not a widely accepted agreement among headache specialists with regards to the optimal GON block methodology, such as used injecting technique, type and doses of the local anaesthetics and corticosteroids (Tobin and Flitman, 2009). For example, the role of corticosteroids in this setting is still debated (Caputi and Firetto, 1997; Ashkenazi and Young, 2005).

The specific conditions treated with GON block vary and include both primary (e.g. migraine, cluster headache) and secondary (e.g. cervicogenic) headache disorders (Ashkezani et al, 2010). Despite favourable outcomes reported by many practitioners, there is still a relative lack of scientific evidence and data (Young et al, 2008; Tobin and Flitman, 2009). Most studies are small sample size, heterogeneous sample groups, limited by retrospective design and lack of control arm. Moreover methodology used varies greatly, making generalisation and comparison of the results difficult. Sitting up following a GON block procedure is currently considered the standard way of managing a patient, however studies do not actually specify this within their methodology. This prospective randomised controlled multi-centre trial evaluates whether the patient's positioning following GON block affects the efficacy of the treatment in terms of achieving a headache-free period and overall degree of headache relief.

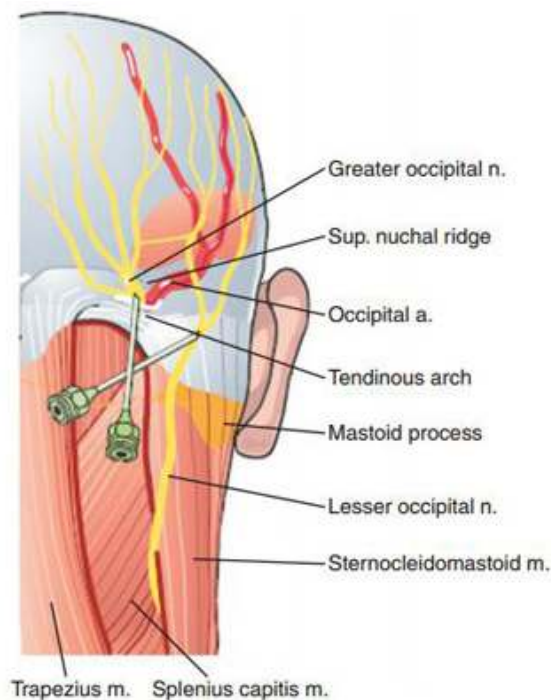
### **2.2 GON block rationale and mechanism of action**

The rationale for using GON block as a treatment for headache comes from the proximity of sensory neurons in the upper cervical spinal cord to trigeminal nucleus caudalis (TNC) neurons and the convergence of sensory input to TNC neurons from both cervical and trigeminal fibres. The evidence for this comes from several studies. In an animal study,

stimulation of the GON was shown to increase metabolic activity in the TNC, as well as in the upper cervical dorsal horn (Goadsby et al, 1997). The same neural sites are activated after mechanical or electrical stimulation of trigeminal nerve innervated structures, such as the superior sagittal sinus (Goadsby and Zagami, 1991). These observations suggest that a convergence of sensory input from cervical and trigeminal afferents occurs at the level of the second order afferent neurons in the TNC. In further support of this hypothesis, Bartsch and Goadsby (2002) demonstrated in a rat model of cranial nociception that dorsal horn neurons at the C2 level respond to stimulation of both the dura and the GON. Moreover, stimulation of the GON facilitates C2 neuronal response to dura mater stimulation. In accordance with these data, it has been shown in humans that GON block may result in alleviation of pain even outside of the skin territory supplied by the nerve (Peres et al, 2002).

There is no standard protocol for Greater Occipital Nerve block procedure. The usual procedure – used in Cumbria Partnership NHS FT and in this present study - consists of inserting a 23-gauge needle into at the medial third of the distance between the occipital protuberance and the mastoid process (Figure 1) and infiltrating the nerve with a local anaesthetic (2% Lidocaine) with a corticosteroid (Depo-Medrone 80 mg). GON block is an easy-to-perform and relatively economical procedure with a favourable safety profile that can be performed in an outpatient clinic setting.

**Figure 1: Anatomy of the Occipital nerves**

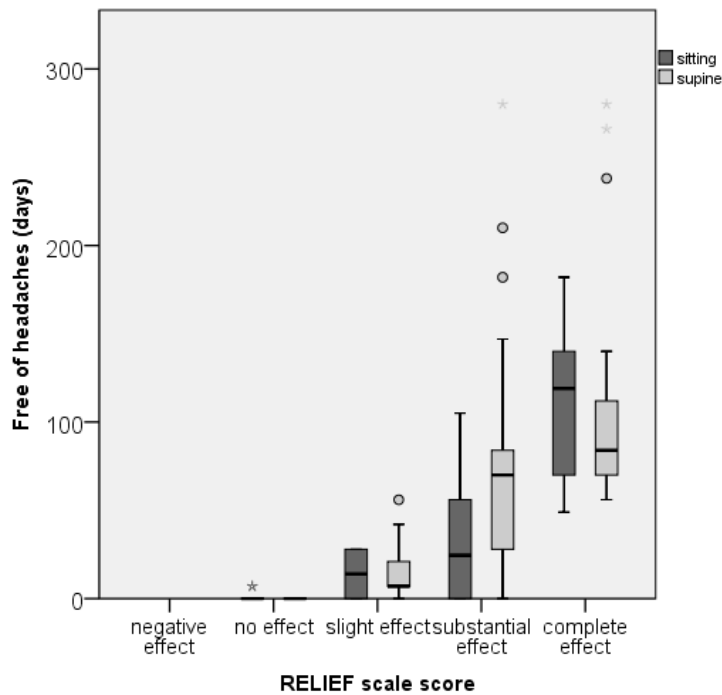


### 2.3 Efficacy of GON block and results from patient-position pilot study

There is a wide variety in response rates to GON block. The published response interval lies between a few days and 3 months. Afridi reported that in migraine patients yield a complete or partial response that lasted - for the partial response - a median of 30 days. For cluster headache, 13 of 22 injections yielded a complete or partial response lasting for a median of 21 days for the partial response (Afridi et al, 2006). Tobin identified 21 articles researching benefit of GON block and found that the duration of reported benefit was between 1-4 weeks in most studies. The reported benefit did not exceed median of 32 days after a single treatment in any of the studies (Tobin and Flitman, 2009).

At a local level, a pilot study (submitted for publication) has revealed that for those patients who follow the standard protocol for GON block, ie sitting down after the procedure, the median achieved headache-free period is 7 days. The headache-free period is 56 day for those patients who lie down (supine) for 10 minutes following GON block (see also Figure 2). In this study, a mix of primary headache disorders was included in the respective cohorts. Table 1 shows that the diagnosis does not affect the headache-free period achieved. Only chronicity of the condition (negatively) and the patient's position (positively for supine) were significantly associated with the achieved headache-free period.

**Figure 2: Headache-free days after GON block for Cumbrian patients, stratified by RELIEF score**



**Table 1: backward multiple linear regression analysis: headache-free period (days) as dependent**

<b>Variable</b>	<b>Beta</b>	<b>p-value</b>
Sex	-0.089	0.43
Patient age (yrs)	-0.020	0.86
Chronicity of condition	-0.21	0.12
History of GON block	0.069	0.54
Main diagnosis	-0.043	0.74
Baseline headache severity	0.033	0.77
Baseline headache duration	-0.054	0.65
Baseline headache frequency	0.11	0.34
Patient position post-GON	0.23	0.041*
<b>Most significant variables</b>		
Chronicity of condition	-0.24	0.024*
Patient in supine position post-GON	0.25	0.018*

\*statistically significant correlation (p-value < 0.05)

## 2.4 Aims and hypothesis

We hypothesise that a patient placed in a horizontal (supine) position for 10 minutes directly after the GON block will prolong duration of the procedure's benefit from the procedure compared to a patient seated up (sitting). GON block has a favourable safety profile and, once a clinician is trained, is an easy-to-perform procedure that can be performed in an outpatient clinic setting. Retaining the patient in a horizontal position for 10 minutes after the procedure does not pose a significant change to the practice, since patients will usually recover for a few minutes anyway whilst seated in the clinic room. This study evaluates whether the patient's positioning following GON block affects the efficacy of the treatment in terms of achieving a headache-free period and overall degree of headache relief.

The null hypothesis is that the supine position is no different from the sitting position in terms of the achieved headache-relief following GON block. Using the RELIEF scale, non-responders are those classed as 'worsening of symptoms', 'no relief', or 'slight relief'. Responders will be those who indicate at follow-up that GON block gave them 'substantial' or 'complete' relief.

### 3. INTERVENTION & DEVICE USE

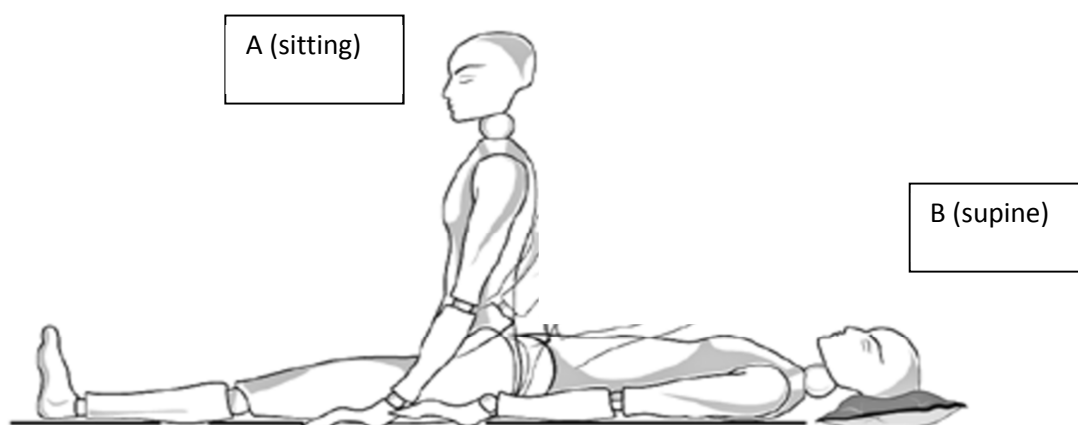
#### 3.1 Intervention

All participants will be given single treatment unilateral or bilateral GON block, inserting a 22-23 gauge needle, using dose of Lidocaine 2% (20mg) with Depo-Medrone (80mg) in 2 ml vial, injected close to GON output (1/3 of distance between external protuberance and mastoid process).

The intervention is as follows: directly following conclusion of the GON block procedure the patient will either

- A. Remain seated vertical (sitting)
- B. Lie horizontally in a supine position for 10 minutes (with head rested on pillow at appr 30 degree angle, see Figure 2), measured with stopwatch.

**Figure 3: patient position options (determined by randomisation) following GON block**



#### 3.2 Medical device used in the study: Curelator app

The Curelator App will be used as a tool to record Patient-Related Outcome Measures (PROMs). Curelator (<https://curelator.com/>) was initially designed to identify triggers and protectors of migraine attacks. On a daily basis, headache patients can record if they have any headache episodes and if there were any factors that may contribute to said episode, such as change in weather, menstrual cycle, exercise, sleep quality etc. For this present study, the trigger/protector element will not be used.

Curelator will be used primarily to allow participants to record :

- Headache(-free) days.

- Severity of headache episodes
- Symptoms related to headache episodes.

If they do have a headache, Curelator will be used prospectively to record the headache symptoms, including severity and length of the episode. To date, virtually all trials for headache treatments have used a paper diary. The paper approach is prone to bias, non-compliance and reliance on patient recall. Therefore, the use of Curelator is a novel approach to recording headache frequency and characteristics.

The user data for all participants will be available to the research team and neurologists via a Curelator dashboard. This will allow interpretation of the data for individual and collective patients. Furthermore, it can be used during the baseline period to ensure that the participant is compliant and sufficient data is collated prior to GON block. This is essential to allow comparison of headache symptoms pre- and post-GON block. Curelator complies with applicable UK data protection laws and regulation.

### 3.2.1 Using Curelator Headache.

Patients will record their headache frequency and intensity, in addition to other symptoms using Curelator Headache™.

Curelator Inc. (Cambridge USA) has developed a proprietary, non-pharmaceutical, digital platform, called Curelator Headache to collect daily data, identify potential trigger-attack associations and propose 'tests' of trigger modification. The underlying premise is that individual's knowledge about their triggers and which, when modified or avoided, affect their condition, empowers the individual to better manage their lifestyle so as to improve their quality of life and reduce healthcare utilization.

The Curelator approach requires high quality data from the individual, entered on a daily basis. Hence Curelator has developed a quick, easy to use, customized user interface and it is expected that with this a high degree of compliance with, and adherence to, many weeks of data entry can be achieved. Compliance is expected to be enhanced because the study is being offered by the individual's healthcare provider.

**Curelator Headache** currently consists of multiple, linked components:

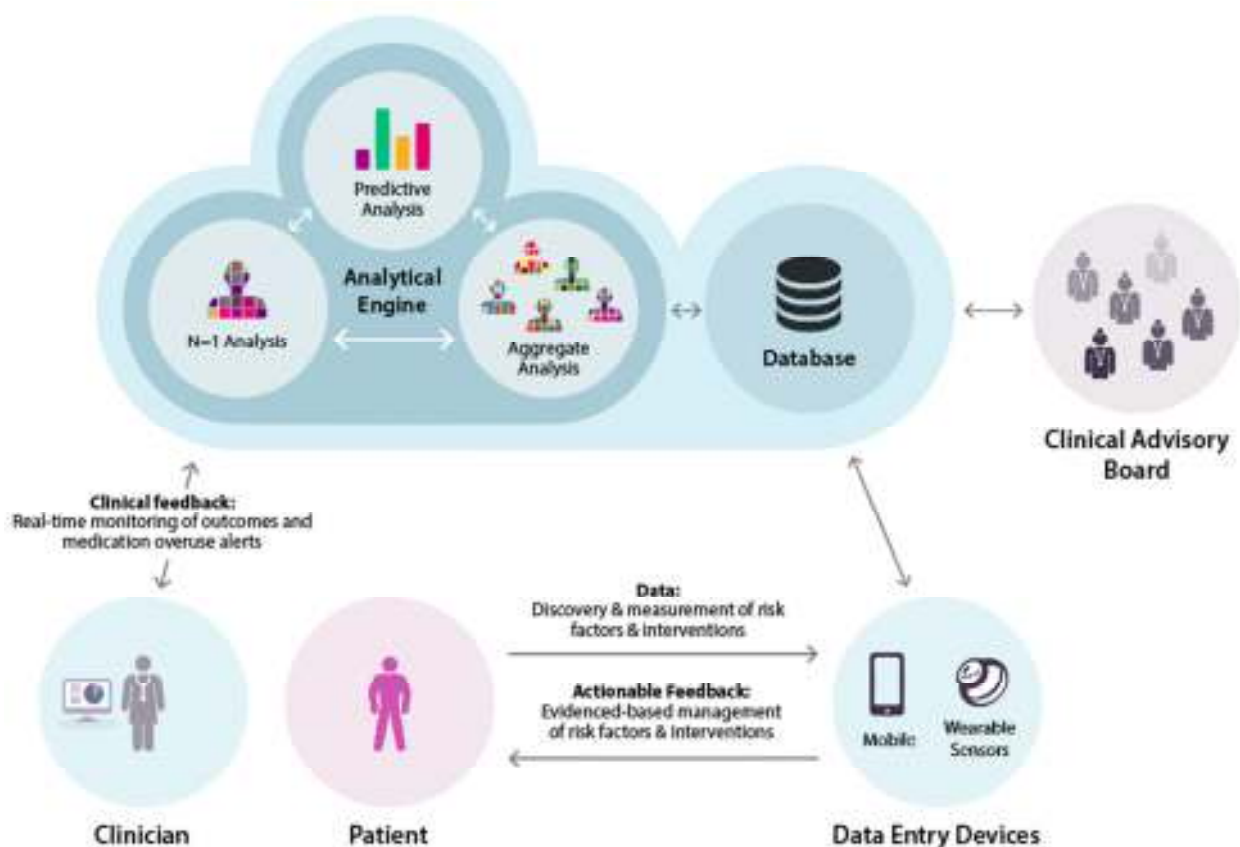
1. A **website** that informs visitors about Curelator Headache and how to sign up as a clinical trial subject or user.
2. A **Web based process** to set up users with a username and secure password and a secure on-line registration process (termed 'onboarding') during which users are assessed regarding eligibility criteria, informed about the study, informed consent

can be obtained, and also demographic and relevant medical history data is collected.

3. An **app** which runs on iPhones and iPads (compatible with iOS 9 and above), and other compatible smartphones/tablets (Android 4.1 and above). Using this, data are entered about headaches and about daily behaviours and exposure to possible migraine triggers, via a series of questions. **Daily questions modules will be pre-configured for this study, in agreement with the Chief Investigator.**
4. A **secure database** hosted in a HIPAA compliant datacenter which is maintained by a third-party company which specialises in data security and compliance (Armor Defense Inc., Richardson, Texas, USA)
5. Data processing, statistical analysis and display algorithms located on multiple devices. These use **anonymized** data exported from Curelator's secure database. Processed data are reimported to the database and re-linked to user identification so that processed information can be sent to the user.
6. Users visualize their personal information via the app or secure web access. They can also print or export their data to other devices and email so that, for example, they can share it with their clinician. Users also grant permission to their clinicians to view data collected and run basic analysis on a secure web platform for physicians (Physician dashboard).
7. A password-protected **Physician dashboard** through which the study doctor invites study subjects to use Curelator Headache as part of the study procedures. Through the dashboard the doctor can monitor subject progress and review the subjects data and reports.

The platform is illustrated below:

#### **Figure 4. Risk associated with Curelator Headache use**



Use of Curelator Headache is not expected to pose any risk to patients. Proposed test interventions are limited to diet modification (for example avoidance of certain foods, alcohol, caffeine) and environmental factors (for example bright lights, loud noises) and guidance on lifestyle interventions (for example stress management and sleep hygiene) and implementing the protective factors. Curelator Headache may also identify signs in individuals that warn of an impending attack (for example neck pain, sensitivity of skin on the head): individuals may use this information to modify their behaviour to minimise the impact of an attack.

Curelator Headache is NOT for the purpose of diagnosing headache type and will NOT propose any medication changes.

Expected benefit is that Curelator Headache will identify one or more associations between potential triggers, warning signs, premonitory symptoms and/or protective factors and the occurrence of migraine attacks. At the end of the 90 day period Curelator will inform subjects about such associations, via their personal 'trigger map'. Subjects will be able to produce succinct reports for their physician, which include visualisations of headache events over the study period, the trigger map and other data that may be clinical useful. These



outputs of Curelator will empower subjects to improve self-management and facilitate clinical management of their condition and aid physicians in treating their patients.

Subjects who stop entering daily data will receive reminders. If no data are entered for 14 days they will be sent a brief questionnaire asking if they no longer wish to enter data and, if so, the reasons for stopping use. No further follow up will be conducted.

## **4. STUDY OBJECTIVES**

### **4.1 Primary objective**

The primary objective is to determine if there is any difference in headache RELIEF score post-GON block intervention, as recorded by patients at 90 days post-intervention. The first 24 hours after GON block are excluded to avoid patients recording GON block procedure-specific headache as a regular headache episode.

### **4.2 Secondary objective**

Any difference in headache RELIEF score post-GON block intervention, as recorded by patients at 30 days post-intervention.

Any difference in number of headache-free days post-GON block intervention (as recorded by patients using the Curelator headache app and retrospective recall) at 30 days and 90 days post-GON block compared to baseline 30 days data and between intervention arms.

Any change in headache severity, related symptoms (such as aura, photophobia), frequency and duration – baseline 30 days versus follow-up 90 days and between intervention arms (recorded by patients using Curelator).

Correlation for headache-free days comparing Curelator recordings vs patient retrospective recall.

Any change in headache-related quality of life, as measured with patient-reported outcome measures (validated questionnaires HIT-6, MIDAS, MSQ).

Any change in prophylactic and/or rescue medication use, and its potential economic impact.

Analysis of variables that may be associated with favourable outcomes after GON block through multi-regression analysis

## 5. STUDY PROTOCOL

### 5.1 Study design, recruitment sites and timeline

This concerns a multi-centre, controlled, prospective, randomised trial. The study will be carried out in the following NHS Trusts:

- Cumbria Partnership NHS Foundation Trust, Neurology Department, Penrith, CA11 8JA, UK
- City Hospitals NHS Sunderland Foundation Trust, Neurology Department, Sunderland, SR4 7TP, UK
- Hull and East Yorkshire Hospitals NHS Trust, Hull Royal Infirmary, Anlaby Rd, Hull HU3 2JZ
- Newcastle upon Tyne Hospitals NHS Foundation Trust, Royal Victoria Infirmary, Newcastle, NE1 4LP, UK

The study will take place in an out-patient clinic room setting with support and oversight from the treating neurologist, nursing staff and research staff. Where appropriate, research delivery staff will be delegated to provide support with data collection and processing.

**Table 2: Anticipated timeline for PARAGON trial**

Month	Setup	Recruitment	Analysis	Finalise
Jun-18	Submission for ethics/HRA approval			
Jun-18	NIHR portfolio adoption			
Aug-18	Ethics/HRA and Trust approval			
Sep-18		Start recruitment		
Jun-19		Finish recruitment		
Sep-19			Follow-up complete; Analyse data.	manuscript & report writing

### 5.2 Participant identification and research setting

Participants will be recruited from neurology clinics and all eligible patients will be invited to take part until the required numbers have been achieved. Identification will be by the neurology clinical team, supported by the research staff. A screening form will be completed for potentially eligible patients to confirm that they indeed meet the trial criteria.

To summarise, the neurologist team will:

- Identify potentially eligible patients and ask verbal consent for them being approached about the study by a member of the R&D team
- Complete the incl/excl criteria part of the screening form (if a patient has given verbal consent to being approached by the research team then they can complete the screening form)

### **5.3 Consent and recruitment**

Those eligible will be approached and provided with an information pack and consent form. If a patient wishes to participate, the consent form will be signed to indicate that informed consent has been given. Patients will be given ample time to consider taking part, more than 24 hours if they wish. However, if the patient is comfortable with the study and fully understands what it entails then they are allowed to provide written informed consent within 24 hours.

The study will be first mentioned at a neurology out-patient clinic visit. The direct healthcare professional will first approach a patient about the study, and after verbal consent by the patient the healthcare professional themselves or a member of the research team can go through the informed consent process.

As mentioned, patients are allowed to consent to taking part when first approached as long as the study has been discussed with the patient and they have been given time to read the patient information leaflet and had an opportunity to ask any questions that they may have. Participants will receive no incentives (apart from free use of the Curelator app) and consent will be regarded as a process and not a one-off event. Participants are free to withdraw from the study at any time without the need to give any reasons for withdrawal. Their standard of care will not be affected by either declining to participate in the study or withdrawing during participation. Data collected up to the date of withdrawal will be retained for analysis.

Since GON block application may be dependent on the operator, block randomisation will be applied to ensure that one supine position patient will be recruited for each sitting position patient (stratified by migraine/other condition).

### **5.4 Follow-up**

Patients are in the study for a period of approximately 17 weeks – this includes 30 days before GON block and 90 days after the procedure. For Cluster Headache the baseline Curelator App recording period will be shorter at 14 days. Thereafter, the patient will be followed up as they would be in normal clinical practice. Study visits are aligned to hospital/clinic visits where possible and will take place remotely too where possible.

Baseline data is collected for a period of 30 days before the GON block procedure (14 days for Cluster Headache patients due to debilitating nature of their active phase and need for urgent GON block intervention), and Curelator data can commence up to 60 days prior to the planned GON block date (30 days for Cluster Headache patients). Participants are only randomised to one of the two intervention arms if they are compliant in daily use of the Curelator app (ie also when they do not have a headache, so that reliable data is collected). Unlike with a paper diary, there is no way of cheating and completing the diary at a later date. The Curelator dashboard will be used to monitor compliance; to ensure sufficient data is collated, participants must complete the diary 80% of days before the GON block appointment (equal to  $\geq 24$  out of 30 days minimum, or  $\geq 12$  out of 14 days for Cluster Headaches).

For the 30 day and 90 day follow-up appointments, data can be collected in person to coincide with a clinic visit if applicable, over the phone, via e-mail or by mail (whichever is preferred by the patient – mail is by use of freepost, to avoid patients incurring any costs). The researcher will phone/e-mail/mail the participant at 30 days and 90 days post-GON block to ensure the patient reported outcome measures are collected, and also to check on any adverse event reporting. The follow-up procedures are the same for all types of headache conditions.

#### **5.4.1 Blinded assessment for follow-up visits**

The treating neurologist will not conduct the follow-up questionnaires with the participants. A researcher or nurse who has not witnessed the actual GON block procedure and does not know the position that the participant was placed in post-GON block will conduct the follow-ups. This only applies if the participants prefers to do the follow-up visits over the phone, rather than being sent the questionnaires via post or e-mail.

### **5.5 Outcome measures**

#### **5.5.1 Primary outcome measures**

- RELIEF score at 90 days post-GON block; the score will also be recorded at 30 days post-GON block

#### **5.5.2 Secondary outcome measures**

- Headache-free period post-GON block in days
- Average monthly headache days (before GON block and post-GON block)
- Severity of headache (severe, moderate, mild, none)

- Headache characteristics
  - o Including aura, photophobia
- Average length of each headache episode in hours
- Impact of headache disorder on quality of life
  - o HIT-6, modified MIDAS, MSQ (latter for migraineurs only), see Appendix 4
- Prophylactic and/or rescue medication use
  - o Total cost of medicine use (before GON block and post-GON block), using British National Formulary as source for costs.
- Adverse event reporting by participants

All the outcome measures are summarised in Table 3.

**Table 3. Overview of measurements**

Item / timing	-30 days to day 0 GON block*	GON block to 10 min post-GON block	30 days post-GON block#	90 days post-GON block##
<b>Baseline demographics</b>	X			
<b>Curelator diary</b>	X		X	X
<b>VDS pain scale</b>		X		
<b>Headache characteristics questionnaire</b>	X		X	X
<b>PROMs (HIT6, MIDAS, MSQ)</b>	X		X	X
<b>Medication use</b>	X			X
<b>Headache-free days (patient recall)</b>			X	X
<b>RELIEF score</b>			X	X
<b>Curelator feedback questionnaire</b>				X
<b>Safety recording</b>			X	X

\* Allowed to be up to 30 days early

# Allowed to be up to 7 days early and 14 days late

## Allowed to be up to 14 days early and 28 days late

## 6. SUBJECTS

### 6.1 Anticipated number of research subjects

Patients will be recruited from the adult (age 18+) population routinely seen by the evaluating clinical staff members. The sample size calculations are based on results from a pilot study on patient positioning and GON block.

The non-parametric Chi-squared test is used and 80% power and 5% significance is applied. A priori power calculations using GPower 3.1 software, result in the following sample size

summarized in Table 4. It also shows the number of responders and non-responders per patient position.

The sample size calculation also takes into account a 30% patient attrition rate (withdrawal due to non-compliance with Curelator App before GON procedure and loss to follow-up), since this involves a study with multiple timepoints for data collection up to 90 days. Furthermore, in the pilot evaluation we observed a 10% drop-out rate and Curelator was not used in that study.

In order to be able to analyse a pure subset of subjects with migraine, the samples size will take into account a ‘migraine only’ sample and a ‘other headache disorders’ sample – with each having a 1:1 randomised distribution of sitting and supine participants. Analysis will be performed on an intention-to-treat basis – ie lost participants post-GON block will be classed as a non-responder.

**Table 4: Sample size calculation based on data from pilot study**

<b>RELIEF score</b>	<b>sitting</b>	<b>Supine</b>
Non-responders (no relief, slight relief)	18 (53%; 12 no relief, 6 slight)	17 (28%; 8 no relief, 9 slight)
Responders (substantial relief, complete relief)	16 (47%; 10 substantial, 6 complete)	44 (72%; 27 substantial, 17 complete)
total	34	61
<p>Power beta of 80%, Alpha p-value of 0.05, Effect size 0.50</p> <p>Sample size required without any drop-out: 32 subjects.  Sample size with 30% attrition rate included: 42</p> <p>Total of 42 migraine patients:  21 Patients in sitting position  21 Patient in supine position</p> <p>Total of 42 patients with other headache type:  21 Patients in sitting position  21 Patient in supine position</p> <p>Overall total: 84</p>		

The CONSORT guidelines require a statement on the number of patients assessed for eligibility (Schulz, Altman & Moher 2010), see also Appendix 3. The number of patients screened but who did not meet the inclusion criteria or who declined to participate will be recorded, as will any patients who are lost to follow-up.

### 6.1.1 **Randomisation**

Following written consent, participants are allocated at random to the control or Coban intervention group, using a randomised sequence from the freeware randomisation programme, see <https://www.randomizer.org/> . Block randomisation, blocks of 6 patients to be allocated each time to a recruitment site, will be undertaken to ensure even distribution of cases from different clinicians into the two arms. Randomisation will also be stratified by cohort (migraine vs non-migraine cohorts).

Sequential envelopes with each next randomisation allocation will be used to achieve concealment and these will be kept in the research department. The researcher or regular healthcare professional for the participant in question can e-mail ([research@cumbria.nhs.uk](mailto:research@cumbria.nhs.uk)) or phone the R&D Dept (01228 602173) to determine which treatment the next participant has been allocated to. At this stage the Curelator dashboard will also be checked for baseline diary compliance.

## 6.2 **Eligibility criteria**

### 6.2.1 **Inclusion criteria**

- Diagnosis fulfilling IHS criteria for primary headache disorder, which includes:

For migraine cohort:

- episodic or chronic migraine

For non-migraine cohort

- occipital neuralgia,
  - cluster headache,
  - trigeminal autonomic cephalgia (TAC)
  - non-specified or other primary headache disorder
- Deemed eligible for GON block procedure as determined by treating neurology team
  - Aged 18 or older
  - Mental capacity to give written informed consent

### 6.2.2 **Exclusion criteria**

- Under the age of 18 years
- Unable to fully understand the consent process and provide informed consent due to either language barriers or mental capacity

- Any condition that precludes patients from receiving GON block, including:
  - Disorders associated with excessive bleeding, coagulation abnormalities or any other significant haematological condition (e.g. Factor V Leiden, haemophilia, thrombocytopenia).
  - Known acute or previous base of skull fracture
  - Allergy or hypersensitivity to any active ingredients or excipients used for GON block
- Patients who are participating in another interventional research study involving an investigational product related to their headache disorder.
- The patient has concurrent (medical) conditions that in the opinion of the investigator may compromise patient safety or study objectives.
- Subjects who have received greater occipital nerve blocks (both GON or Botox) in the last 6 months, or are still headache-free following an intervention.
- For randomisation after baseline period:
  - Less than two headache episodes in baseline 30 day data collection period
  - Curelator App used < 25 days out of 30 day baseline diary period

### 6.3 Early withdrawal of subjects

Patients have the right to withdraw from the trial at any time and without giving any reason. If a patient withdraws from the trial, any and all information gathered prior to the withdrawal will be used in the analysis, but no further data collection will occur. If a patient does not attend a planned follow-up appointment then two more attempts will be made to contact the patient regarding the study. If still no contact can be made then the patient is deemed lost to follow-up and any collected study data will be retained.

## 7. SAFETY

### 7.1 Potential risks & benefits to study participants

There is no anticipated personal safety risk associated with taking part in this study. The only study intervention is the difference in patient position post-GON block. If the research team learns of important new information that might affect the patient's desire to remain in the study, he or she will be told. Appropriate precautions are in place to ensure medical and personal information is kept safe through adhering to appropriate governance regulations. Any adverse events will be recorded, as outlined in sections below. Only adverse events that may occur in the 10 minute intervention period (ie sitting or supine following GON block) will be considered for safety reporting as part of the trial. As part of the trial, any other reported wider GON related issues will be recorded but are not deemed an AE.

Participants cannot claim payments, reimbursement of expenses or any other benefits or incentives for taking part in this research.

### 7.2 Safety definitions



Adverse Event (AE)	<p>Any untoward medical occurrence in a patient or other clinical investigation participant taking part in a trial of a medical device, which does not necessarily have to have a causal relationship with the device under investigation.</p> <p>An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom or disease temporally associated with the use of the procedure, whether or not considered related to the procedure.</p>
Serious Adverse Event	<p>A serious adverse event is any untoward medical occurrence that:</p> <ul style="list-style-type: none"> <li>results in death</li> <li>is life-threatening</li> <li>requires inpatient hospitalisation or prolongation of existing hospitalisation</li> <li>results in persistent or significant disability/incapacity</li> <li>consists of a congenital anomaly or birth defect.</li> </ul> <p>Other 'important medical events' may also be considered serious if they jeopardise the participant or require an intervention to prevent one of the above consequences.</p> <p>NOTE: The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.</p>

### 7.3 Procedures for recording adverse events

All AEs need to be reported to the sponsor/host Trust R&D **within ten working days** of the investigator team becoming aware of them. For this purpose an AE report form is completed by the researcher and/or Chief Investigator

The relationship of each adverse event to the trial must be determined by the Chief Investigator, a medically qualified individual, according to the following definitions:

- **Related:** The adverse event follows a reasonable temporal sequence from swabbing. It cannot reasonably be attributed to any other cause.
- **Not Related:** The adverse event is probably produced by the participant's clinical state or by other modes of therapy administered to the participant.
- **Severity grading:** the Chief Investigator will also record if it concerns an AE or SAE.

This is recorded on the aforementioned AE reporting form. The forms are stored in the study site file.

Pseudo-anonymised copies of all adverse events forms will be shared with Curelator as soon as causality reporting has been performed and concluded.

## **8. STATISTICAL CONSIDERATION AND DATA ANALYSIS PLAN**

### **8.1 Analysis of baseline characteristics**

To determine the demographics and characteristics of the patients in the two arms the following data will be collated:

- Age (yrs)
- Gender
- Height (kg), weight (cm), BMI
- Headache disorder diagnosis
- Typical location of headache pain
- Chronicity of headache disorder
- Use of prophylactic and/or rescue medication

Any differences in distribution will be established with Chi-squared test or Mann-Whitney U-test/t-test (depending on distribution of data) as indicated.

### **8.2 Primary outcome statistics**

To compare outcomes between the two groups (treatment response for sitting vs supine position post-GON at 90 days), Chi-squared test will be applied.

### **8.3 Secondary outcome statistics**

The average baseline demographics for participants in each group will be compared to ascertain that randomisation has indeed led to comparable distribution of participants:

Sex, age, height, weight, BMI, use of prophylactic and or rescue medication, type of headache disorder, chronicity of headache disorder, headache severity score, headache frequency score, average length of headache episodes, number of headache days, type of headache disorder (chronic vs episodic for migraine cohort and different headache disorders for non-migraine cohort).

To compare outcomes between the two groups (treatment response for sitting vs supine position post-GON at 30 days), Chi-squared test will be applied.

To compare headache-free outcomes between the two groups (headache-free days for sitting vs supine position post-GON), Mann-Whitney U-test will be applied. Although it will

likely apply, skewness in the distribution of data will first be assessed with the Shapiro Wilk test. This analysis will be done for: the migraine cohort, non-migraine cohort, and cohorts combined.

For the PROMs, Mann-Whitney U-test will be applied.

Cox proportional hazards regression analysis will be conducted to investigate the role of post-GON patient position and other covariates (as mentioned above) in post-GON severity/frequency/length of headaches, headache-free days and on the RELIEF score.

Any impact of having undergone previous GON block on headache frequency, duration, symptoms and severity will be analysed too through regression analysis.

## **9. DATA HANDLING AND MONITORING**

Data arising from this study is confidential. Identifiable information can only be accessed by delegated members of the study team. Anyone in the research team who does not have a substantive contract with Cumbria Partnership NHS Trusts or one of the recruiting NHS Trusts will need to apply for a letter of access via the NIHR research passport scheme, should they require access to identifiable study data.

Patient identifiable data will only be used within each respective Trust and by the core research team. All identifiable data is stored on password protected NHS computer systems. Anonymised data will be shared and stored using security-enabled systems such as password-protection and encryption of e-mails and files (including the use of nhs.net for correspondence via e-mail). The requirements of the Data Protection Act and NHS Code of Confidentiality will be followed at all times. All researchers will be fully trained in NHS Confidentiality and GCP. Participants' GP practices will be informed that they are taking part in the study.

All paper data will be held in secure locked environments in the office of the Research & Development and Neurology department of Cumbria Partnership. Data released (e.g. by publication) will contain no information that could lead to the identification of an individual participant. Similar arrangements are to be made by any other participating recruitment site. Upon completion of the study the site files will be archived for a period of 15 years in line with local archiving policy and procedures. Direct access to data only will be granted to authorised representatives from the sponsor / host institution and the regulatory authorities to permit trial-related monitoring, audits and inspections.

This investigator-initiated trial will be monitored in terms of conduct of the study by the in-house research team, led by the Chief Investigator, who will convene on a monthly basis in person or via phone/e-mail. A formal trial steering committee will not be convened for this

trial – however, when data is available for 50% of the sample an interim analysis will take place to assess if there are any points of concern to consider. The study can be audited by the in-house R&D department as part of their rolling audit programme of sponsored and hosted research studies. As part of the research grant agreement, anonymised study data will be shared with Curelator Inc for review and for potential publication purposes. No identifiable data, will be contained in any of this data. However, as part of signing up to the Curelator App, the participants' e-mail address will be shared with Curelator. They will not pass this information on to third parties.

## **10. GOVERNANCE OF STUDY**

### **10.1 Approvals**

This study will be conducted in compliance with the protocol approved by the Health Research Authority, National Research Ethics Service, and local Trust R&D Approval, and according to Good Clinical Practice standards including the Declaration of Helsinki (1964, Amended Oct 2013). No deviation from the protocol will be implemented without the prior review and approval of the aforementioned review bodies, except where it may be necessary to eliminate an immediate hazard to a research subject. In such case, the deviation will be reported according to policies and procedures.

### **10.2 Sponsor & Indemnity**

Cumbria Partnership NHS Trust is the sponsor of this study and therefore NHS indemnity applies for design, conduct and management of the study. Curelator Inc has provided a grant for this study by means of provision of the Curelator App free of charge for each participant (for the duration of the trial) and a research grant worth £1,000.

Patients will not be given financial incentives for taking part in the study. Travel expenses are not offered in this study since patients are not seen in clinic more frequently than they would normally attend as part of their normal care pathway – Patient visit 3 at 30 days post-GON block is a remote visit where patients will complete questionnaires from their own home. Participants will be given access to the Curelator app free of charge.

## **11. PUBLICATION AND DATA-SHARING POLICY**

The study will be registered on ISRCTN or Clinical Trials Gov website, in line with CONSORT guidelines on good practice in clinical research (see Appendix 2).

The results of this study are planned to be disseminated through:

- Peer-reviewed manuscript in scientific journal
- Presentation and/or poster at a scientific conference
- Internal report to the funder of the trial, Curelator

As stated in the PIL and ICF, anonymised study data will be shared with Curelator as part of the research grant agreement.

A summary of the main findings can be supplied to participants on request and this will be stated in the informed consent form.

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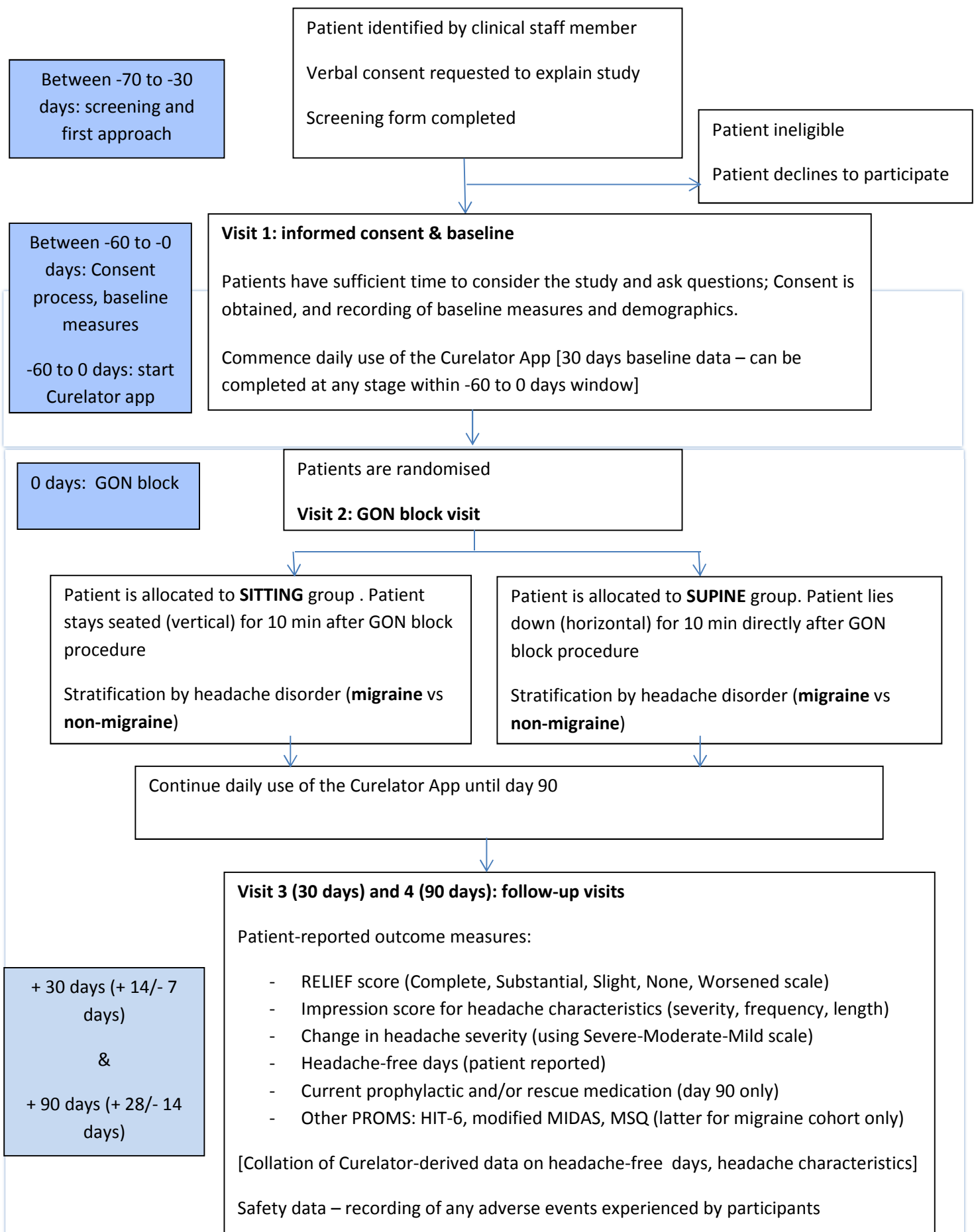
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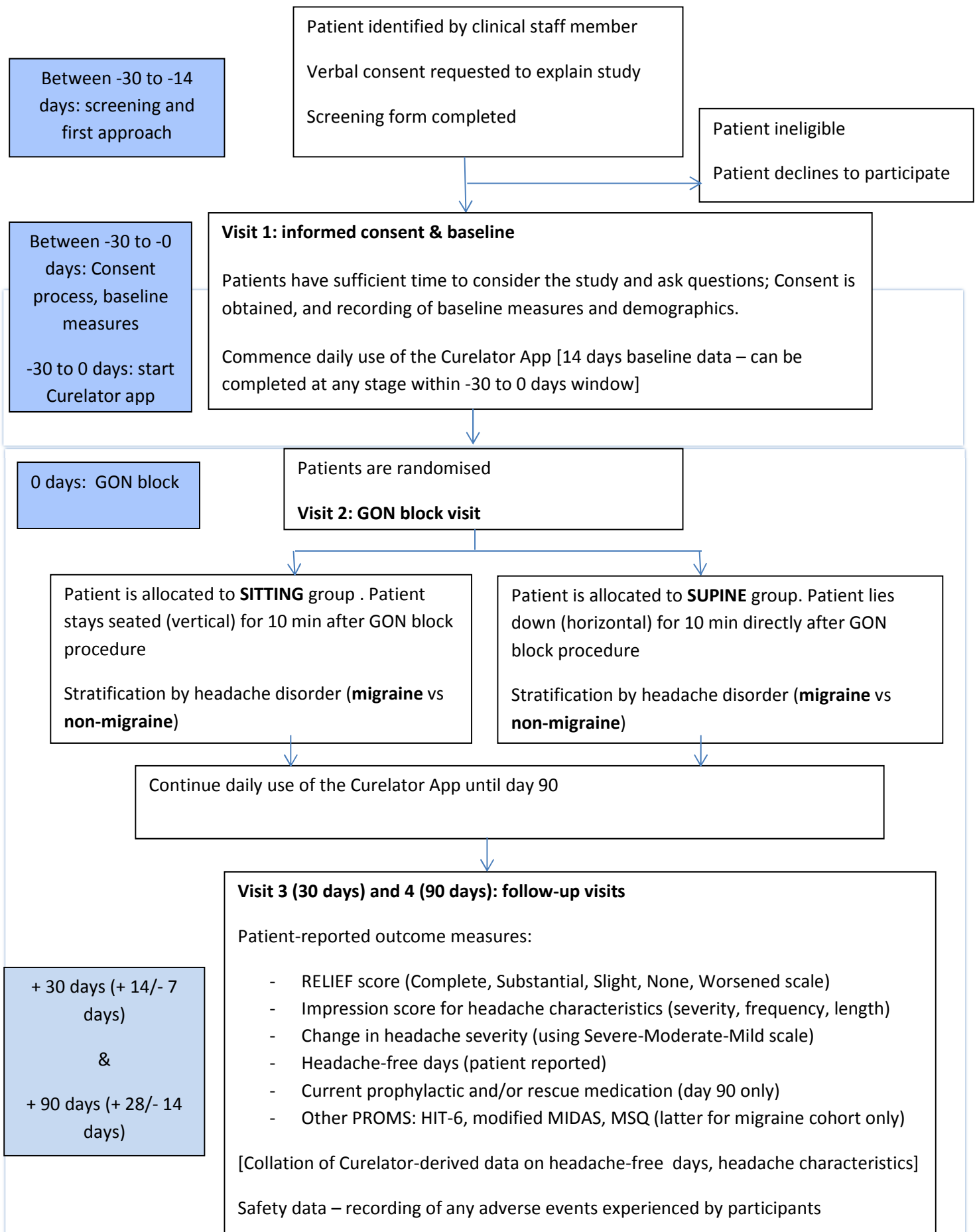
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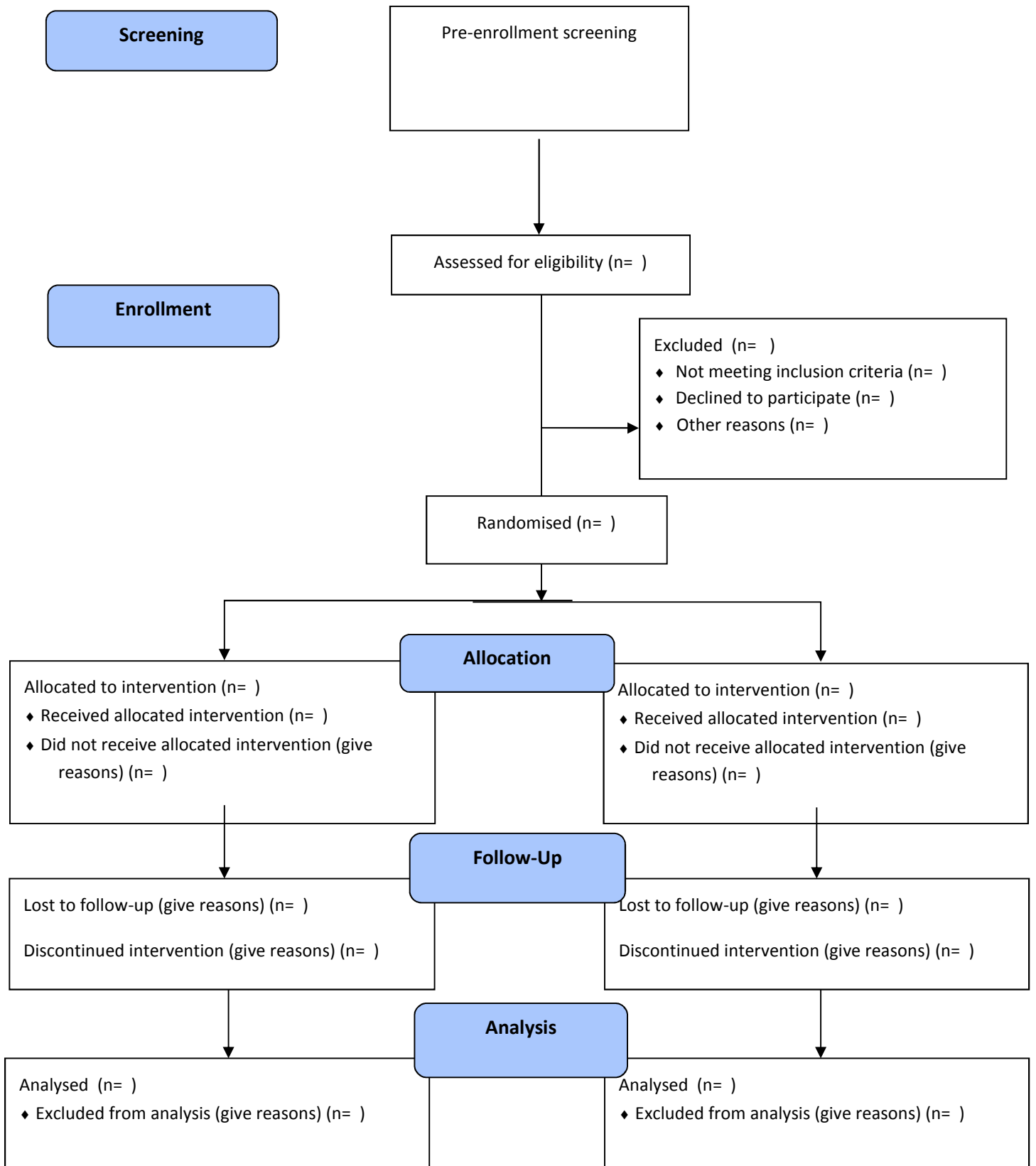
## APPENDIX 1, STUDY PARTICIPANT FLOWCHART



## APPENDIX 2, STUDY PARTICIPANT FLOWCHART – CLUSTER HEADACHE



## APPENDIX 3, CONSORT FLOW DIAGRAM OF PARAGON STUDY



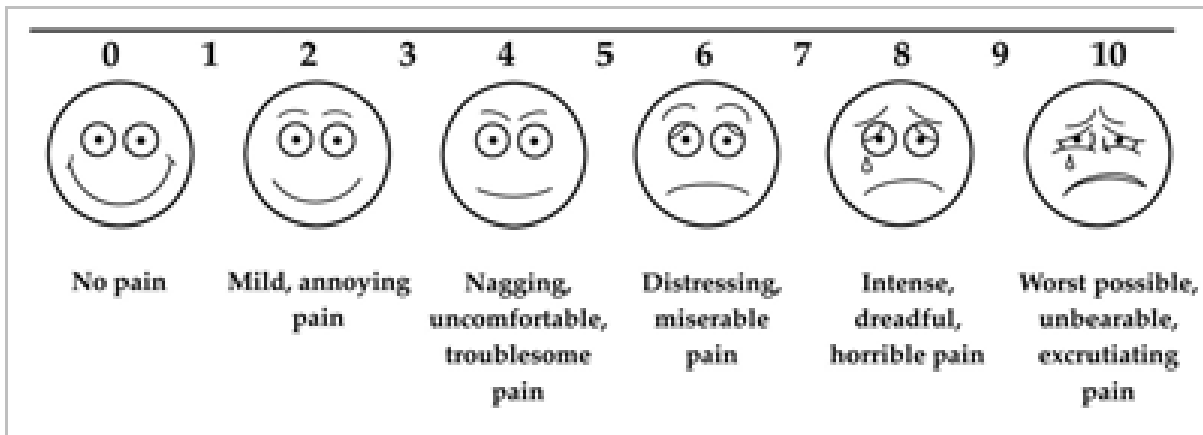
## **APPENDIX 4, VALIDATED PATIENT REPORTED OUTCOME MEASURES**

- Visual Display Pain scale
- RELIEF scale (headache pain relief scale)
- HIT-6
- Modified MIDAS
- MSQ (for migraine cohort only)

### Visual Descriptor Pain score

To be measured 10 minutes after the GON block procedure

How painful was GON block procedure:



Please put a vertical line on the numbered bar above.

We kindly ask you consider the procedure as a whole and to summarise the discomfort/pain with one number.

**RELIEF scale – headache pain relief scale.**

Since the GON block procedure, what has generally been the degree of headache pain relief you have experienced?

<b>Tick one box please</b>	<b>Description</b>
	Pain has worsened
	No relief
	Slight relief
	Substantial relief
	Complete pain relief

## HEADACHE IMPACT TEST HIT-6™ (HIT-6)

This questionnaire was designed to help you describe and communicate the way you feel and what you cannot do because of headaches.

To complete, please tick one box for each question.

1. When you have headaches, how often is the pain severe?

Never Rarely Sometimes Very Often Always

2. How often do headaches limit your ability to do usual daily activities including household work, work, school, or social activities?

Never Rarely Sometimes Very Often Always

3. When you have a headache, how often do you wish you could lie down?

Never Rarely Sometimes Very Often Always

4. In the past 4 weeks, how often have you felt too tired to do work or daily activities because of your headaches?

Never Rarely Sometimes Very Often Always

5. In the past 4 weeks, how often have you felt fed up or irritated because of your headaches?

Never Rarely Sometimes Very Often Always

6. In the past 4 weeks, how often did headaches limit your ability to concentrate on work or daily activities?

Never Rarely Sometimes Very Often Always

HIT-6™ (Headache Impact Test™) © 2000, 2017 QualityMetric Incorporated and the GlaxoSmithKline Group of Companies. All rights reserved.

## MODIFIED MIDAS

Please answer the following questions about ALL of the headaches you have had over the last 1 month. Enter zero if you did not do the activity in the last 1 month.

1. On how many days in the last 1 month did you miss work or school because of your headaches? .....|\_|\_| days
2. How many days in the last 1 month was your productivity at work or school reduced by half or more because of your headaches? (*Do not include days you counted in the previous question where you missed work or school.*) .....|\_|\_| days
3. On how many days in the last 1 month did you **not** do household work because of your headaches? .....|\_|\_| days
4. How many days in the last 1 month was your productivity in household work reduced by half or more because of your headaches? (*Do not include days you counted in the previous question where you did not do household work.*) .....|\_|\_| days
5. On how many days in the last 1 month did you miss family, social or leisure activities because of your headaches? .....|\_|\_| days

This survey was developed by Richard B. Lipton, MD, Professor of Neurology, Albert Einstein College of Medicine, New York, NY, and Walter F. Stewart, MPH, PhD, Associate Professor of Epidemiology, Johns Hopkins University, Baltimore, MD.



## MIGRAINE SPECIFIC QUALITY OF LIFE QUESTIONNAIRE (VERSION 2.1) (MSQ)

### PATIENT INSTRUCTIONS:

Please fill out this questionnaire. It will help us understand the effects of migraine on your daily activities.

The questionnaire has been designed so that it can be completed quickly and easily. Please tick only one answer for each question. You should answer every question.

Thank you for your time.

While answering the following questions, please think about **all migraine attacks** you may have had **in the past 4 weeks**.

1. In the past 4 weeks, how often have migraines **affected** your relationships with your family, friends and others who are close to you? (Select only **one** response.)

- 1  None of the time
- 2  A little bit of the time
- 3  Some of the time
- 4  A good bit of the time
- 5  Most of the time
- 6  All of the time

2. In the past 4 weeks, how often have migraines **interfered** with your leisure activities, such as reading or exercising? (Select only **one** response.)

- 1  None of the time
- 2  A little bit of the time
- 3  Some of the time
- 4  A good bit of the time
- 5  Most of the time
- 6  All of the time

3. In the past 4 weeks, how often have you had **difficulty** in performing work or daily activities because of your migraine(s)? (Select only **one** response.)

- 1  None of the time
- 2  A little bit of the time
- 3  Some of the time
- 4  A good bit of the time
- 5  Most of the time
- 6  All of the time

4. In the past 4 weeks, how often did migraines **keep you** from getting as much done as you usually do at work or at home? (Select only **one** response.)

- 1  None of the time
- 2  A little bit of the time
- 3  Some of the time
- 4  A good bit of the time
- 5  Most of the time
- 6  All of the time

5. In the past 4 weeks, how often did migraines **limit** your ability to concentrate on work or daily activities? (Select only **one** response.)

- 1  None of the time
- 2  A little bit of the time
- 3  Some of the time
- 4  A good bit of the time
- 5  Most of the time
- 6  All of the time

6. In the past 4 weeks, how often have migraines **left you too tired** to do work or daily activities? (Select only **one** response.)

- 1  None of the time
- 2  A little bit of the time
- 3  Some of the time
- 4  A good bit of the time
- 5  Most of the time
- 6  All of the time

7. In the past 4 weeks, how often have migraines **made you feel** less energetic? (Select only **one** response.)

- 1  None of the time
- 2  A little bit of the time
- 3  Some of the time
- 4  A good bit of the time
- 5  Most of the time
- 6  All of the time

8. In the past 4 weeks, how often have you **had to cancel** work or daily activities because you had a migraine? (Select only **one** response.)

- 1  None of the time
- 2  A little bit of the time
- 3  Some of the time
- 4  A good bit of the time
- 5  Most of the time
- 6  All of the time

9. In the past 4 weeks, how often did you **need help** in handling routine tasks (such as every day household chores, personal business, shopping, or looking after others), when you had a migraine? (Select only **one** response.)

- 1  None of the time
- 2  A little bit of the time
- 3  Some of the time
- 4  A good bit of the time
- 5  Most of the time
- 6  All of the time

10. In the past 4 weeks, how often did you have to **stop** work or daily activities to deal with migraine symptoms? (Select only **one** response.)

- 1  None of the time
- 2  A little bit of the time
- 3  Some of the time
- 4  A good bit of the time
- 5  Most of the time
- 6  All of the time

11. In the past 4 weeks, how often were you **unable to participate** in social activities such as parties or dinner with friends, because you had a migraine? (Select only **one** response.)

- 1  None of the time
- 2  A little bit of the time
- 3  Some of the time
- 4  A good bit of the time
- 5  Most of the time
- 6  All of the time

12. In the past 4 weeks, how often have you **felt** fed up or frustrated because of your migraines? (Select only **one** response.)

- 1  None of the time
- 2  A little bit of the time
- 3  Some of the time
- 4  A good bit of the time
- 5  Most of the time
- 6  All of the time

13. In the past 4 weeks, how often have you **felt** that you were a burden on others because of your migraines? (Select only **one** response.)

- 1  None of the time
- 2  A little bit of the time
- 3  Some of the time
- 4  A good bit of the time
- 5  Most of the time
- 6  All of the time

14. In the past 4 weeks, how often have you been **afraid** of letting others down because of your migraines? (Select only **one** response.)

- 1  None of the time
- 2  A little bit of the time
- 3  Some of the time
- 4  A good bit of the time
- 5  Most of the time
- 6  All of the time

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