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# Prophylactic effect of music therapy on episodic migraine patients under the care of chronic pain department

MusicMig

## PROTOCOL OF STANDARD CARE EVALUATION

Version n°1.0 dated of 21/09/2018

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## DOCUMENT HISTORY

VERSION	DATE	REASON OF CHANGE

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**SIGNATURE PAGE OF THE PROTOCOL**

**« Prophylactic effect of music therapy on episodic migraine patients under  
the care of chronic pain department »**

***MusicMig***

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## 1. PROTOCOL SYNOPSIS

<b>ADMINISTRATOR</b>	CHU de La Réunion – Site of GHSR
<b>RESEARCH RESPONSIBLE</b>	Emmanuelle De Diego PH Algology Responsible of Chronic Pain Service Group of Hospital South Réunion University Hospital Centre of Reunion
<b>TITLE</b>	Prophylactic effect of music therapy on episodic migraine patients under the care of chronic pain department.
<b>VERSION</b>	1.0
<b>JUSTIFICATION / CONTEXT</b>	Music therapy has been validated in the management of chronic pain and anxiety disorders. A program of music therapy will be proposed by the CHU Chronic Pain department team from GHSR. The objective of this study is to evaluate the effect of the music in the migraine specific indication.
<b>OBJECTIVES</b>	<p><b><u>Principal objective</u></b> To evaluate the effect of music therapy on migraine frequency, on patients suffering from episodic migraines and followed in chronic pain department of the CHU Sud Reunion.</p> <p><b><u>Secondary objectives</u></b> To evaluate the effect of music therapy on migraine intensity, duration, and acute treatment administration. To evaluate the effect of music therapy on emotional effect (HAD score) and functional impact (HIT-6 score).</p>
<b>STUDY DESIGN</b>	Prospective study of before-after type. It is composed of only one group of patients, all treated with music. The study will measure and compare migraine frequency in the month before the intervention with data collected 3 months after.
<b>INCLUSION CRITERIA</b>	<ul style="list-style-type: none"> <li>- patients aged <math>\geq 18</math> years</li> <li>- patients with episodic migraine (&lt;15 days / month) with at least 4 crises per month.</li> <li>- patients with migraines with or without aura with diagnostic criteria per International Headache Society</li> <li>- patients with a migraine for more than one year</li> <li>- diagnosis age &lt; 50 years</li> <li>- patients with an available internet connexion to access Music Care application</li> <li>- patients with minimal knowledge in informatics</li> <li>- patients who sign their inform consent</li> </ul>
<b>EXCLUSION CRITERIA</b>	<ul style="list-style-type: none"> <li>- patients aged less than 18 years</li> <li>- patients with chronic migraine</li> <li>- patients with epilepsy</li> <li>- patients with a deficiency on auditive function</li> <li>- patients with a disease that could be fatal within the study period.</li> </ul>

<b>STANDARD CARE NATURE EVALUATED IN THIS RESEARCH</b>	Sessions of music therapy self-directed by the patient at home, using Music Care software via an internet connexion.
<b>EVALUATION CRITERIA</b>	<p><b>Primary evaluation criterion</b> Reduction of migraine frequency of 50% after 3 months.</p> <p><b>Secondary evaluation criteria</b> Reduction of migraine intensity and duration, as well as acute treatment administration. Reduction of the emotional and functional impact.</p>
<b>PLANNED SAMPLE SIZE</b>	20 patients
<b>PLANNED CENTERS</b>	1 centre: Chronic Pain Department of CHU-GHSR site of Saint-Louis
<b>DURATION OF THE RESEARCH</b>	<ul style="list-style-type: none"> <li>- Duration of inclusion period: 1 month</li> <li>- Duration of patient participation: 3 months</li> <li>- Total duration of the study: 4 months</li> </ul>
<b>STATISTICAL ANALYSIS</b>	<p><b>Analysis of the primary endpoint</b> The mean number of migraine crises per month before and after music therapy will be compared using the Wilcoxon Paired Test.</p> <p><b>Analysis of secondary endpoints</b> Quantitative variables before and after music therapy will be analysed using Wilcoxon Paired Test. Qualitative variables will be analyzed using McNemar Chi<sup>2</sup> test.</p>
<b>EXPECTED RESULTS</b>	<p>To propose a new therapeutic and non-drug approach in episodic migraine prophylaxis.</p> <p>To improve the relationship between medical team and patients.</p> <p>To reduce the treatment consumption.</p>

## 2. SCIENTIFIC JUSTIFICATION

Migraine is a frequent pathology, it affects 20% of the French population and represents 1 milliard euros of direct cost. It is a research topic largely studied under non-drug approaches. The ANAES provided in its migraine recommendations in October 2002 to use relaxation, biofeedback and stress management cognitive and comportemental therapies in the care of migraine patients.

Music therapy is a recent discipline with a trend of development in hospital services and in specialised ambulatory care centres. Several controlled studies allowed to validate the utilisation of music therapy in chronic or sharp pain, as well as in anxio-depressive disease. In this domain, the work of Stephane Guetin, psychologist and music therapist, helped using Music Care software to elaborate a standardised computerised method allowing its use by caregivers and patients themselves.<sup>1, 2, 3</sup>

Researches on music therapy effect on migraine patients are few.

A first German study in 1999 evaluated the effect of *Psychophonia* software on migraine, informatic tool which build a sound sequence from EEG of the patient. This cohort study on 55 adult migraine patients showed a decrease of at least 50% of migraine crises in 56% of patients treated for 12 months.<sup>4</sup>

A second German study in 2008 evaluated the effect of active music therapy and the use of butterbur root extract (Petalodex) in the prevention of child migraine. This randomised, controlled study based on 58 patients distributed under 3 arms (music therapy/ butterbur/placebo) demonstrated superiority of music therapy arm against placebo after 8 weeks, and the superiority of the 2 treatments against placebo at 6 months.<sup>5</sup>

The demonstrated effects of music therapy on chronic pain and anxio-depressive disease allow to assume a benefic effect of this technique in the migraine.

Scientific data of music therapy on migraine patients are positive and suppose its interest in this indication, as in chronic pain, but additional and more specific studies are needed to evaluate its indication on this specific pathology. A clinical study with 2 arms might be helpful.

The standardised and validated music therapy technique named as *Music care* seems to be a useful tool in standard cares and clinical research.

### 2.1. CURRENT STATE OF KNOWLEDGE

#### 2.1.1.ON THE PATHOLOGY

Episodic migraine is defined as several days with crisis < 15 days / month.<sup>6</sup>

Its prevalence is equal to 12% to 20% in the general French population, so 7 million of migraine patients, with more women (ratio of 1/3).

This pathology starts before 40 years with high anxio-depressive comorbidity due to possible pathophysiologic community.<sup>7</sup>

It is an under-diagnosed pathology, with only 30% of migraine followed patients.

The disease consequences are functional disability, current activities reduced in 70% of migraine patients.

The social impact cost is estimated to 1 milliards euros / year and 15 million of loosed days of work / year.

Fifty percent of the patients used auto medication with a risk of drug abuse and evolution to chronic migraine (> 15 days of crisis / month).<sup>8</sup>

#### 2.1.2.ON THE STRATEGIES/REFERENCE PROCEDURES

Recent clinical and neurophysiological studies made it possible to highlight the positive effect of music therapy in pain treatment<sup>9</sup>. Causing relaxation, music decreases painful phenomena in patients with

chronic and sharp pain. By shifting the attention, music decreases muscular tension and reduces anxiety. In pre and postoperative pains, patients under music decreased their drug consumption up to 30%. The effects of music therapy are generally related to the fact that the individualized music broadcasting improves interactive components of pain. The impact of music therapy might be due to neurophysiologic effects, specific to pain, and to the music effect on sensory (attenuation of the conduction of afferent fibres), cognitive (memory encoding, diverts attention), affective (stimulates the production of endorphins) and behavioural (psychomotricity, muscular hypertonia) components. The effect of the music therapy is based on the impact of music on the components of the painful experience and the modification of pain perception.

Psychological factors can interfere in the reduction of chronic painful phenomenon: music is chosen by the patient with his personal preferences, it allows to respond to an individual listening request. Listening to the patient after the music session allows him to evacuate their tensions.

Several controlled studies demonstrated that receptive music therapy and more specifically psychomusical relaxation has an efficacy on several painful pathologies like dental, obstetrical, cancerous, chirurgial, neurological, rheumatic and et functional. <sup>10, 11, 12, 13, 14</sup>

## **2.2. RESEARCH HYPOTHESES**

The study is based on the hypothesis of a prophylactic effect of music therapy on migraine disease using its action on the 4 components: sensory, affective, behavioural and cognitive.

## **2.3. NATURE OF STANDARD CARES EVALUATED IN THE RESEARCH**

Music therapy sessions are based on the use of Music Care software. It is software developed by the music therapist psychologist S. Guetin. Ten services in CHU GHSR will be equipped of it and their teams will be trained to it under the framework of the institutional training plan. This project has been proposed by Dr E De Diego responsible of Chronic Pain Department GHSR and supported by CLUD GHSR.

Among concerned services, Chronic Pain Department GHSR will propose standard cares by music therapy for chronic migraine patients.

## **2.4. JUSTIFICATION OF METHODOLOGIC CHOICES**

This study has been designed as a before-after study without control group. Intervention being realized under current practice, it will not be possible to propose a randomised trial with one arm is treated with music therapy and another one not.

The month before inclusion will serve as reference. Effect of music therapy will be evaluated during 3 months after inclusion, using a period of same duration of the reference one and using the same tools.

During the 3 months, patients will be followed every month during a visit realised at Chronic Pain Department of GHSR in order to evaluate if the patient is compliant in completion of migraine diary, uses correctly Music Care and if he is compliant with his program. During the visit, migraine evaluation will be evaluated.

## **3. OBJECTIVES**

### **3.1. PRIMARY OBJECTIVE**

To evaluate the effect of music therapy on migraine frequency, on patients suffering from episodic migraines and followed in chronic pain department of the CHU Sud Reunion.

### 3.2. SECONDARY OBJECTIVES

- To evaluate the effect of music therapy on migraine intensity, duration, and acute treatment administration.
- To evaluate the effect of music therapy on emotional effect (HAD score) and functional impact (HIT-6 score).

## 4. STUDY DESIGN

### 4.1. METHODS

Monocentric, prospective before-after study.

It comprises of only one group of patients and all of them will receive the intervention.

The study will measure and compare migraine frequency during the month before inclusion with migraine frequency 3 months after the inclusion.

- **Entry in the study:** based on proposition of algologist doctor involved in the patient care and after patient receives information and signs inform consent.

- **Inclusion period:** the month before the initiation of music session will serve as reference period. Patient will fill migraine diary, complete questionnaires on functional and emotional impact used usually in the department.

The following endpoints will be evaluated:

- migraine severity (number of days with migraine, duration, intensity, treatment)
- questionnaire HAD to evaluate emotional impact
- questionnaire HIT to evaluate functional impact

#### - **Music therapy session implementation**

Each patient will be asked to follow 1 to 2 sessions per day for 3 months, to be done at home, using *music care* software via internet connexion.

They will complete the migraine diary during the 3 months of the study.

They will have a visit at the Chronic Pain Department every month, so at Month 1, 2 and 3, realised by an intern of general medicine.

#### - **Final evaluation at Month 3**

Diary data of the third month will serve for this evaluation according to the guidelines of the International Headache Society:

- number of days with migraine (primary endpoint)
- duration and intensity of migraine
- medication consumption
- emotional impact: score HAD
- functional impact: score HIT.

## 5. ELIGIBILITY CRITERIA

### 5.1. INCLUSION CRITERIA

- patients aged of 18 to 65 years
- patients with episodic migraine (<15 days / month) with at least 4 attacks per month

- patients with migraines with or without aura with diagnostic criteria per International Headache Society
- patients with a migraine for more than one year
- diagnosis age < 50 years
- patients with an available internet connexion to access Music Care application
- patients with minimal knowledge in informatics
- patients who sign their inform consent

## **5.2. NON-INCLUSION CRITERIA**

- patients aged less than 18 years
- patients with chronic migraine
- patients with epilepsy
- patients with a deficiency on auditive function
- patients with a disease that could be fatal within the study period.

## **5.3. PATIENT RECRUITMENT**

The recruitment of the patients will be done at Chronic Pain Department of GHSR site of Saint-Louis during their standard ambulatory care.

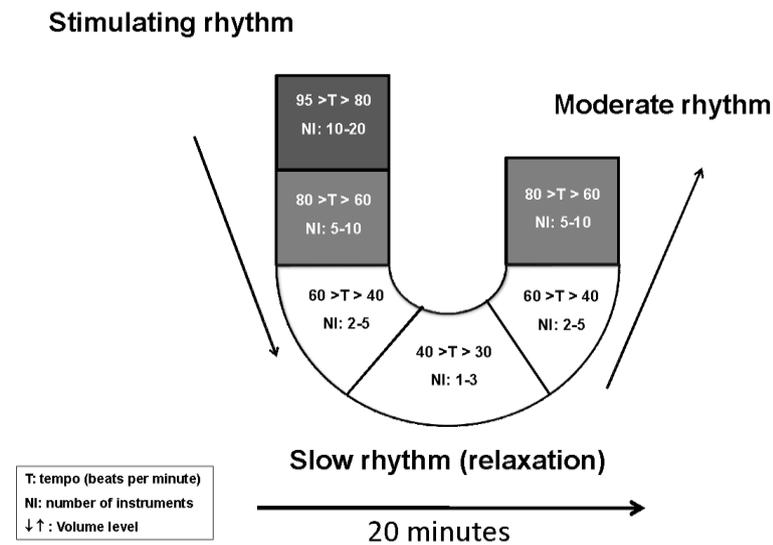
Inclusion and exclusion criteria will be checked by the responsible of the study during the inclusion visit. This study will enrol around 20 patients during a short period of time.

## **6. NATURE OF ROUTINE CARE ASSESSED IN THE RESEARCH**

### **6.1. ACT(S) IN STUDY**

The Music Care app is a receptive music intervention self-directed by the patient at home, allowing the patient to freely adjust the length of and choose the preferred style between different sequences of instrumental music. All musical pieces were recorded in high-quality recording studios with professional musicians. After a formation on how to use the application, the patient will have the possibility to choose, according to his musical preferences, between different music therapy sequences based « U » technique. Music Care utilizes the “U” technique (Figure 1), designed to gradually relax the listener. In the current study, music sequences during patients’ sessions were based on the mount “U”, and instrumental musical works were selected for a varying numbers styles (classical, jazz, world music, etc.) and adapted to the patient's style via patient request. The “U” technique is implemented using a musical sequence of 20 minutes that was divided into 5 different musical pieces at 3 to 4 minutes each. Initially, the objective is to represent the patient's state of tension by stimulating musical rhythm (80-95 beats per minute (bpm). From there, the remaining 4 sub-pieces are presented in a blended fashion in an attempt for the patient to gradually fall into a relaxed state via a gradual reduction in musical tempo (40-80 bpm), orchestral size, frequencies, and volume (descending arm of the “U”). The music session then reaches a phase of maximum relaxation (downward phase of the “U”) before a phase that gradually returns to baseline dynamics (ascending arm of the “U”).

Figure 1: The “U” sequence



Headphones were required (provided at time of treatment), and patient were instructed to lay down (to promote muscle relaxation) with their eyes closed and lighting to a minimum. Participants answered questions related the frequency, duration, and other migraine related questions throughout the treatment. At the end of the 3-month of treatment, participants underwent the same assessment as at baseline.

The objective of 1 to 2 daily sessions will be suggested to the patients according to their availability. Migraine crisis frequently implies a phonophobia, so it will be recommended to realise the sessions outside migraine crisis. As patient will manage his sessions as he wants, this information will be given without contraindicating music therapy during crisis if patient wants to do it.

The training to *Music care* software for the doctors in charge of the study will be done by a music therapist from AM-ARC, with a validated diploma and experience in clinical research, under the framework of the institutional training plan of the CHU.

## 7. EVALUATION CRITERIA

Primary and secondary endpoints are defined according to the last recommendations related to the evaluation of prophylactic migraine treatment of ANAES October 2002<sup>15</sup>: « *Treatment is considered as efficient if crisis frequency is reduced of at least 50 %. It is also important to consider the reduction of medication consumption, intensity and duration of crisis. Evaluation is done after 3 months.* ». The methodology is consistent with guidelines of International Headache Society for clinical research on migraine.<sup>16</sup>

### 7.1. PRIMARY ENDPOINT

**Reduction of migraine crisis frequency of at least 50% after 3 months of treatment.**

The studied variable will be the monthly frequency of migraine crisis. Data collection will be done using a migraine agenda (annex 1), starting the month before inclusion and music therapy initiation. This agenda

should then be completed usually during study period under music therapy. During each monthly visit, a control will be done by the intern of general medicine associated to the study.

The primary endpoint will be obtained using the difference between mean crisis frequency during the month before music therapy initiation and the one obtained during the 3rd month of treatment.

A reduction of at least 50% at month 3 will be considered as music therapy efficacy on episodic migraine prevention.

## 7.2. SECONDARY ENDPOINTS

### - Reduction of crisis intensity and duration, as well as medication consumption.

Crisis intensity (mild, moderate, severe), duration in hour, and the number of treatments taken will be collected in the migraine agenda (annex 1) filled by the patient. These variables will be compared between the month before music therapy initiation and the 3rd month of treatment.

### - Reduction of functional and emotional impact.

Questionnaires HAD and HIT (annex 2) will be completed with the investigator during the inclusion visit before initiation of music therapy, and at Month 3 visit.

- Questionnaire HAD to evaluate emotional impact (national reference HAS « chronic pain: recognize chronic pain syndrome, evaluate it and guide the patient »)<sup>17</sup>
- Questionnaire HIT to evaluate functional impact (guideline of the International Headache society)<sup>18</sup>

## 7.3. ESTIMATED TIMELINES OF THE RESEARCH

- Start of inclusion: November 2018
- Duration of retrospective observational period: 1 month
- Duration of patient participation: 3 months
- Total duration of the study: 4 months

## 7.4. SUMMARY TABLE OF PATIENT FOLLOW-UP

	Screening visit M-1	Inclusion visit Day 0	Month 1 visit	Month 2 visit	Month 3 visit
Patient information	✓				
Training on agenda migraine completion	✓				
Training on <i>Music care</i> use		✓			
Inform consent collection		✓			
Diagnosis questionnaire		✓			
Check on number of music sessions			✓	✓	✓
Check on migraine agenda completion		✓	✓	✓	✓
Questionnaires HAD et HIT		✓			✓

Screening visit will be done by the medical responsible of the study, PH algologist. Inclusion and follow-up visits will be also done by the investigator.

All the visits will be performed at Chronic Pain Department of CHU-GHSR site of Saint-Louis.

Follow-up visits will be done monthly after inclusion visit with a window of +/- 1 week.

## 7.5. SCREENING VISIT

Screening visit will be managed by the algologist responsible of the study. It will be done between 4 months and 1 month before inclusion visit.

### 7.5.1. PATIENT INFORMATION

During screening visit and before any evaluation or data collection, the investigator will inform the patient of the study and propose him to participate. The following points will be described:

- Objectives and design of the study,
- Data collection and processing, access rights.

Migraine agenda (usually used by the team) will be provided to the patient in order to complete the 1-month observational period.

During this visit, inclusion and exclusion criteria will be verified. If the patient agrees to participate, oral consent will be provided.

## 7.6. INCLUSION VISIT

During this visit, a complete information on objectives and course of the study is provided to the patient. Informed consent is collected by the algologist investigator of the study.

Diagnosis questionnaire, and HAD and HIT questionnaires HAD et HIT are completed with the investigator. Migraine agenda to be filled during the next 3 months is provided to the patient.

A training to *Music care*, music therapy software, is realized by the study responsible. Details on methodology, objectives of the technique, as well as the optimal conditions of use are given to the patient. During this visit, the first music session is done at the hospital under medical control. A questionnaire is filled in order to have a better knowledge of migraine patient about music preferences likely to bring him to relaxation.

A secure account is created to allow patients to have a free internet access and use *Music care* during the study.

At the end of this visit, the patient should be able to use at home by himself the software and to realize music therapy sessions using *Music care*.

## 7.7. FOLLOW-UP VISITS

Follow-up visits will be monthly done by the investigator, at Month 1, Month 2 and Month 3 after inclusion. During these visits, checks will be done regarding agenda migraine completion, patient motivation will be evaluated, and the number of music sessions done will be collected.

Impressions and feeling of the patient regarding music sessions will be collected.

## 7.8. END OF STUDY VISIT

This final visit corresponds to the follow-up visit at Month 3. Final data collection on migraine agenda will be realized as well as HAD and HIT questionnaires filled with the algologist.

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## 7.9. SPECIAL MODALITIES OF CARE

Music therapy use does not require special modalities of care.

## 8. GESTION OF SERIOUS ADVERSE EVENTS

No procedure for serious adverse events is imposed by the research. Nevertheless, declaration of serious adverse events to the regional center of pharmacovigilance is mandatory for all doctor and health professional.

## 9. STATISTICAL ASPECTS

### 9.1. SAMPLE SIZE CALCULATION

Primary endpoint is the reduction on migraine crisis frequency before and after music therapy.

In the population of patients corresponding to inclusion criteria, mean number of migraine crisis per month can be estimated to 8 (standard deviation = 4) before intervention.

A reduction clinically significant would be a reduction of at least 50% of mean monthly number of migraine crisis after 3 months of care.

Under these conditions, 20 patients are needed to have this difference of 50% with a statistical power of 90% and an alpha equal to 5%.

### 9.2. STATISTICAL METHODS

#### Baseline characteristics

Baseline characteristics will be summarized. Qualitative variables will be described using number of patients, percentage and 95% confidence interval (IC95%). Quantitative variables will be described as number of patients, mean, standard deviation, confidence interval of the mean, median, Q1, Q3, minimum and maximum.

#### Analysis of primary endpoint

Monthly mean number of migraine crisis before music therapy will be compared to the one obtained at Month 3 using Wilcoxon signed rank test for paired (dependent samples). The analysis will be performed in intent-to-treat.

#### Analysis of secondary endpoints

Quantitative variables measured before music therapy will be compared with the ones collected after music therapy using the same statistical method as for primary endpoint.

Qualitative variables (proportions) measured before music therapy will be compared with the ones collected after music therapy using McNemar Chi<sup>2</sup> test.

All the tests will be realized with SAS 9.2 software with  $\alpha = 5\%$ . A statistical analysis plan will be prepared and will detailed the different analyses.

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## **10. SOURCE DATA AND DOCUMENTS ACCESS RIGHTS**

### **10.1. DATA ACCESS**

The administrator is in charge to obtain the agreement of all the parties implicated in the research in order to guarantee direct access to source data, reports and documents everywhere the study is conducted in case of quality control and audit.

Corresponding people will provide documents and individual data if requested to the person authorized to access them to follow laws and regulations in place.

### **10.2. SOURCE DATA**

Source data or document is defined as any original document which allow to demonstrate the existence, or the accuracy of a data collected during the research.

Source documents come from:

- Case Report Form
- Questionnaires filled during inclusion visit: diagnosis, HAD and HIT impact
- Migraine diary, filled the month before inclusion and during 3 months under intervention
- End of study questionnaires: HAD and HIT

### **10.3. DATA CONFIDENTIALITY**

In accordance with the law in force, persons with direct access to the source data shall take all necessary precautions to ensure the confidentiality of the information relating to the search, the persons to whom they belong, as regards their identity and the results obtained. These individuals, along with those who direct and oversee the research, are subject to solicitor-client privilege.

During or at the conclusion of the research, data collected on those who are suitable for it and transmitted to the administrator by those who direct and supervise the research (or any other specialized stakeholders) will be codified. Under no circumstances should the names of the persons concerned, or their addresses be clearly indicated.

Procedures for coding patients:

- only the first letters of the patient's name and first name will be recorded, accompanied by a number indicating the order of inclusion of patients from 01 for the first patient to 20 for the twentieth patient.

The administrator will ensure that each person who is suitable for research has been informed about access to the individual data about them and strictly necessary for the quality control of the research.

## **11. QUALITY CONTROL**

### **11.1. INFORMATION FOR DATA COLLECTION**

All information required by the protocol shall be recorded on the observation books and an explanation shall be provided for each missing data. Data should be collected as they are obtained and transcribed into these books in a neat and legible manner.

Incorrect data found on the observation books will be clearly crossed out and the new data will be copied, next to the crossed-out information, accompanied by initials, the date and possibly justification by the person who is directing and monitoring the research or the authorized person who made the correction.

Data are collected on a paper CRF.

The data to be collected directly in the CRF will be:

- age, sex
- migraine diagnosis according to International Headache Society criteria
- number of days with headache per month
- duration and intensity of crises
- headache treatment medication per month
- HAD and HIT

### **11.2. RESEARCH MONITORING**

The research will be monitored by a clinical research technician. He or she will be responsible for:

- research logistics and monitoring,
- reporting on its progress,
- checking the update of the CRF (request for additional information, corrections, etc.),

He will work in accordance with standard operating procedures, in collaboration with the Clinical Research Associate delegated by the administrator.

### **11.3. QUALITY CONTROL**

A clinical researcher appointed by the administrator regularly visits each center, when the research is set up, once or more in the course of the research according to the pace of inclusions and at the end of the research. During these visits, the following elements will be reviewed:

- compliance with the research protocol, the procedures defined therein and the legal instruments in force,
- quality of the data collected in the CRF: accuracy, missing data, consistency of the data with the source documents (medical records, appointment books, original laboratory results, etc.).

All visits will be subject to a written monitoring report.

### **11.4. DATA MANAGEMENT**

The data will be entered in Excel (or epidata for example). They will be managed by the investigator and stored on the computer server of the CHU de la Réunion, which will safeguard them. The data will be coded and frozen by the Principal Investigator before being forwarded to the Statistical Processing Methodological Support Unit.

### **11.5. AUDIT AND INSPECTION**

An audit may be carried out at any time by persons appointed by the manager and independent of the research managers. Its objective is to ensure the quality of the research, the validity of its results and compliance with the law and regulations in force.

The persons who direct and supervise the research agree to comply with the requirements of the administrator and the competent authority for an audit or inspection of the research.

The audit may apply to all stages of research, from the development of the protocol to the publication of results and the classification of data used or produced in the research.

## **12. ETHICAL AND REGULATORY CONSIDÉRATIONS**

### **12.1. COMPLIANCE WITH REFERENCE TEXTS**

Since the techniques and methods used in this research are usually carried out, it can be used as part of research to evaluate routine care as defined by Law No. 2004-806 of 9 August 2004 (Article L1121-1, paragraph 2 and Article R1121-3 of the Public Health Code).

The administrator and the person(s) who directs and supervises the research undertake that this research will be carried out in accordance with Law No. 2004-806 of 9 August 2004, as well as in accordance with Good Clinical Practice (I.C.H. version 4 of 1 May 1996) and the Helsinki Declaration (which can be found in its full version on the website <http://www.wma.net/en/30publications/10policies/b3/>).

The research shall be conducted in accordance with this Protocol. Except in emergency situations requiring specific therapeutic procedures, the person(s) who directs and monitors the research undertakes to comply with the protocol in every respect.

This research received the favorable opinion of the Committee for the Protection of Persons (CPP) of Bordeaux. This research is covered by the civil liability insurance of the CHU of The Reunion.

The data recorded during this research are computerized at the CHU de la Réunion in compliance with the law no. 78-17 of 6 January 1978 on information technology, files and freedoms as amended by Law 2004-801 of 6 August 2004. The CHU of The Reunion will send a request for an opinion to the Advisory Committee on the Processing of Information in the Field of Health Research (CCTIRS) and a request for authorization to the National Commission of Informatics and Liberties (CNIL).

### **12.2. PROTOCOL AMENDMENT**

Any substantial change, that is to say any change likely to have a significant impact on the protection of persons, on the conditions of validity and on the results of the research, on the interpretation of scientific documents that support the conduct of the research or on the manner in which it is conducted-This is the subject of a written amendment that is submitted to the Manager and the Data Management and Methodology Centre, if applicable, and the latter must obtain, prior to its implementation, a favorable opinion from the CPP.

Substantive changes, that is, those that have no significant impact on any aspect of the research, are provided to the CPP for information purposes.

All amendments are validated by the administrator, and by all research stakeholders involved in the amendment, prior to submission to the CPP. This validation may require the Scientific Committee meeting.

All amendments to the protocol must be brought to the attention of all health professionals who are involved in the research and who are committed to respecting its content.

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### **13. RESEARCH DOCUMENTS AND DATA CONSERVATION**

The following documents related to this research are archived in accordance with Good Clinical Practice:

– By the people who realize the research:

**- for a duration of 15 years following the completion of the research** (research on drugs, medical devices or in vitro diagnostic medical devices or research not related to a product referred to in section L.5311-1 of the Public Health Code)

- Protocol and potential amendments
- CRF (copies)
- Source data of the patients
- All other documents or papers related to the research.

**- where applicable, for a period of 30 years following the completion of the research**

- Original copy of signed informed consent from participants

All these documents are the responsibility of the person conducting the search during the statutory archiving period.

– By the project manager:

**- for a duration of 15 years following the completion of the research** (research on drugs, medical devices or in vitro diagnostic medical devices or research not related to a product referred to in section L.5311-1 of the Public Health Code),

- Protocol and potential amendments
- CRF (original)
- All other documents or papers related to the research.

**- where applicable, for a period of 30 years following the completion of the research**

- A copy of the signed informed consent of the participants
- Documents related to serious adverse events

All these documents are under the responsibility of the project manager for the statutory archiving period.

No movement or destruction shall be carried out without the approval of the manager. At the end of the statutory archiving period, the manager will be consulted for destruction. All data, documents and reports will be subject to audit or inspection.

### **14. PUBLICATION RULES**

#### **14.1. SCIENTIFIC COMMUNICATIONS**

Analysis of the data provided by the centers is carried out by the Methodological Support Unit. This analysis results in a written report that is submitted to the project manager. This report allows the preparation of one or more publications.

Any written or oral communication of the results of the research must receive the prior consent of the person who directs and monitors the research.

The publication of the main results mentions the name of the project manager, of all health professionals who have included or monitored patients in the research. International rules for writing and publishing will be considered (Vancouver Convention, February 2006).

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## 14.2. PATIENTS RESULTS COMMUNICATION

In accordance with Law No. 2002-303 of 4 March 2002, patients are informed, at their request, of the overall results of the research.

## 14.3. DATA CESSION

Data collection and management are carried out by the University Hospital Centre. The conditions for the transfer of all or part of the research database shall be decided by the research manager and shall be the subject of a written contract.

## 15. REFERENCES

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## 16. APPENDICES

### 16.1. APPENDIX 1

#### MIGRAINE DIARY

Please fill in the migraine calendar daily and specify each day:

Migraine

Headache intensity: mild, moderate or severe

Duration in hours of headache

Migraine treatments used

Date	Migraine/tension headache	Intensity	Duration	Treatments
D1				
D2				
D3				
D4				
D5				
D6				
D7				
D8				
D9				
D10				
D11				
D12				
D13				
D14				
D15				
D16				
D17				
D18				
D19				
D20				
D21				
D22				
D23				
D24				
D25				
D26				
D27				
D28				
D29				
D30				
D31				

## 16.2. APPENDIX 2

Please fill the 2 questionnaires below:

### HAD QUESTIONNAIRE

D	A		D	A	
		<b>I feel tense or 'wound up':</b>			<b>I feel as if I am slowed down:</b>
	3	Most of the time	3		Nearly all the time
	2	A lot of the time	2		Very often
	1	From time to time, occasionally	1		Sometimes
	0	Not at all	0		Not at all
		<b>I still enjoy the things I used to enjoy:</b>			<b>I get a sort of frightened feeling like 'butterflies' in the stomach:</b>
0		Definitely as much		0	Not at all
1		Not quite so much		1	Occasionally
2		Only a little		2	Quite Often
3		Hardly at all		3	Very Often
		<b>I get a sort of frightened feeling as if something awful is about to happen:</b>			<b>I have lost interest in my appearance:</b>
	3	Very definitely and quite badly	3		Definitely
	2	Yes, but not too badly	2		I don't take as much care as I should
	1	A little, but it doesn't worry me	1		I may not take quite as much care
	0	Not at all	0		I take just as much care as ever
		<b>I can laugh and see the funny side of things:</b>			<b>I feel restless as I have to be on the move:</b>
0		As much as I always could		3	Very much indeed
1		Not quite so much now		2	Quite a lot
2		Definitely not so much now		1	Not very much
3		Not at all		0	Not at all
		<b>Worrying thoughts go through my mind:</b>			<b>I look forward with enjoyment to things:</b>
	3	A great deal of the time	0		As much as I ever did
	2	A lot of the time	1		Rather less than I used to
	1	From time to time, but not too often	2		Definitely less than I used to
	0	Only occasionally	3		Hardly at all
		<b>I feel cheerful:</b>			<b>I get sudden feelings of panic:</b>
3		Not at all		3	Very often indeed
2		Not often		2	Quite often
1		Sometimes		1	Not very often
0		Most of the time		0	Not at all
		<b>I can sit at ease and feel relaxed:</b>			<b>I can enjoy a good book or radio or TV program:</b>
	0	Definitely	0		Often
	1	Usually	1		Sometimes
	2	Not Often	2		Not often
	3	Not at all	3		Very seldom

Please check you have answered all the questions

#### Scoring:

Total score: Depression (D) \_\_\_\_\_ Anxiety (A) \_\_\_\_\_

**QUESTIONNAIRE HIT**

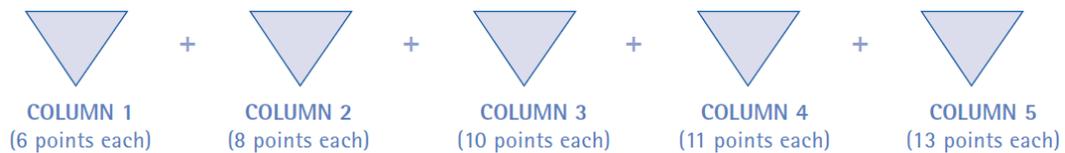
**HIT-6™**  
(VERSION 1.1)

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 circle one answer for each question.



<b>1</b>	<b>When you have headaches, how often is the pain severe?</b>	Never	Rarely	Sometimes	Very Often	Always
<b>2</b>	<b>How often do headaches limit your ability to do usual daily activities including household work, work, school, or social activities?</b>	Never	Rarely	Sometimes	Very Often	Always
<b>3</b>	<b>When you have a headache, how often do you wish you could lie down?</b>	Never	Rarely	Sometimes	Very Often	Always
<b>4</b>	<b>In the past 4 weeks, how often have you felt too tired to do work or daily activities because of your headaches?</b>	Never	Rarely	Sometimes	Very Often	Always
<b>5</b>	<b>In the past 4 weeks, how often have you felt fed up or irritated because of your headaches?</b>	Never	Rarely	Sometimes	Very Often	Always
<b>6</b>	<b>In the past 4 weeks, how often did headaches limit your ability to concentrate on work or daily activities?</b>	Never	Rarely	Sometimes	Very Often	Always



To score, add points for answers in each column.

Please share your HIT-6 results with your doctor.

**Total Score**

Higher scores indicate greater impact on your life.

Score range is 36-78.