Post-Approval Follow-up Study on Sacral Neuromodulation
for the Treatment of Fecal Incontinence

Study Protocol

Version 3,
May 30, 2014
Confidential

Sponsor:
Medtronic International Trading Sàrl
Route du Molliau 31
CH-1131 Tolochenaz, Switzerland
### Signature Page

**Author:**

Claudia Campo  
Name  
Signature  
Clinical Study Manager  
Position  
Date  

**SBU Clinical Management:**

Anne Tille  
Name  
Signature  
Clinical Research Manager  
Position  
Date  

**Medical Affairs:**

Tanja Gabrecht  
Name  
Signature  
Medical Scientific Expert  
Position  
Date  

**Quality:**

Leonie van Meijl  
Name  
Signature  
Clinical QA Specialist  
Position  
Date  

**Regulatory Affairs (France):**

Antoine Audry  
Name  
Signature  
Regional/Local Regulatory Affairs  
Position  
Date  

**Legal Affairs (France):**

Julie Marot  
Name  
Signature  
Senior Legal Manager  
Position  
Date
### History of Changes

<table>
<thead>
<tr>
<th>Protocol version</th>
<th>Protocol date</th>
<th>Description of the changes and reasons</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>November 7, 2012</td>
<td>Initial version</td>
</tr>
<tr>
<td>2</td>
<td>February 15, 2013</td>
<td>Modification of the protocol version number</td>
</tr>
<tr>
<td>2</td>
<td>February 15, 2013</td>
<td>Modification of the page numbers</td>
</tr>
<tr>
<td>2</td>
<td>February 15, 2013</td>
<td>‘Patient consent’ replaced by ‘non-opposition of the patient to the conduct of the study’ in the entire document.</td>
</tr>
<tr>
<td>2</td>
<td>February 15, 2013</td>
<td>‘Neurostimulator’ replaced by ‘Neuromodulator’ in the entire document.</td>
</tr>
<tr>
<td>2</td>
<td>February 15, 2013</td>
<td>The ‘3–6 months’ visit replaced by the ‘4–8 months’ visit in the entire document.</td>
</tr>
<tr>
<td>2</td>
<td>February 15, 2013</td>
<td>The ‘1-year (± month)’ visit replaced by the ‘9–15 months’ visit in the entire document.</td>
</tr>
<tr>
<td>2</td>
<td>February 15, 2013</td>
<td>Initial text of the last inclusion criterion:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>‘treated with InterStim, with an implantation during the inclusion period’</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Text modified:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>‘Patient indicated for the sacral neuromodulation test for InterStim®.’</td>
</tr>
<tr>
<td>2</td>
<td>February 15, 2013</td>
<td>Section ‘Study Population/Treatment’:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Initial text:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>The study sites will have to invite all the patients with a primo-implantation or a replacement implant (reimplantation) to participate in the study if, and only if, a test is performed during the inclusion period.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Text modified:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>The study sites will have to invite all the patients having a primo-implantation or replacement (reimplantation) to participate in the study, in the latter case if, and only if, a test is performed during the inclusion period.</td>
</tr>
<tr>
<td>2</td>
<td>February 15, 2013</td>
<td>Section B.2.1 Description of the Devices:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Model 3889 (quadripolar lead) and Model 3531 (Verify test stimulator) added to the list of devices used in the study.</td>
</tr>
</tbody>
</table>

### SYNOPSIS

**February 15, 2013**

Section ‘Inclusion/Exclusion Criteria’:

*Initial text of the last inclusion criterion:*

‘treated with InterStim, with an implantation during the inclusion period’

*Text modified:*

‘Patient indicated for the sacral neuromodulation test for InterStim®.’

### BACKGROUND

**February 15, 2013**

Section B.2.1 Description of the Devices:

Model 3889 (quadripolar lead) and Model 3531 (Verify test stimulator) added to the list of devices used in the study.

### STUDY DESIGN

**February 15, 2013**

Figure C.1 replaced.

*Initial figure:*
Modified figure:
D SELECTION OF PATIENTS

2 February 15, 2013

Section D.1 Inclusion criteria:

Initial text of the last inclusion criterion:
‘treated with InterStim, with an implantation during the inclusion period’

Text modified:
‘Patient indicated for the sacral neuromodulation test for InterStim®.’

F METHOD

2 February 15, 2013

Table F.1 modified.
### Initial table:

<table>
<thead>
<tr>
<th>VISITS</th>
<th>Screening</th>
<th>Baseline</th>
<th>Test</th>
<th>Implantation Decision</th>
<th>Implantation*</th>
<th>1-3 months*</th>
<th>3-6 months*</th>
<th>1 year (ε±6 months)*</th>
<th>Additional visit</th>
</tr>
</thead>
<tbody>
<tr>
<td>[Day of the study = D]</td>
<td>D (-24)</td>
<td>D-6</td>
<td>D-0</td>
<td>D+22</td>
<td>D+22</td>
<td>52 xD+12</td>
<td>115 xD+262</td>
<td>314 xD+484</td>
<td></td>
</tr>
<tr>
<td>Verbal consent of the patient</td>
<td>x</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Verification of the eligibility criteria</td>
<td>x</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Demographic data</td>
<td>x</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Characteristics of the disease</td>
<td>x</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Surgical and obstetric history</td>
<td>x</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Previous treatments of fecal incontinence</td>
<td>x</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clinical assessment</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Functional assessment</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test data</td>
<td>x</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Implantation data</td>
<td>x</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Multidisciplinary meeting</td>
<td>x</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FIQ</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>WEEVGER</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patient satisfaction</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patient status</td>
<td>x</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stimulation settings</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reimplantation</td>
<td>x</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adverse events</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table F.1: Data to be collected at each visit. Please note that the follow-up visit windows are indicative and will follow the clinical practice of this study site. * Data collected only for the Primary Population; ** Data collected for the Primary Population and Secondary Population.

### Table modified:

<table>
<thead>
<tr>
<th>VISITS</th>
<th>Screening</th>
<th>MC</th>
<th>Baseline</th>
<th>Test</th>
<th>Permanent Implant**</th>
<th>Follow-up visits</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-opposition of the patient to the conduct of the study</td>
<td>x</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Verification of the eligibility criteria</td>
<td>x</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reason for no enrollment*</td>
<td>x*</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Demographic data</td>
<td>x</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Characteristics of the disease</td>
<td>x</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Surgical and obstetric history</td>
<td>x</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Previous FI treatments</td>
<td>x</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clinical assessment (bowel diary and retention period)</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patient satisfaction</td>
<td>x</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wexner incontinence score</td>
<td>x</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FIQ score</td>
<td>x</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Functional assessment</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Specializations represented at the MC</td>
<td>x</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Type of lead implanted</td>
<td>x</td>
<td>x</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Specialization of the operator</td>
<td>x</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Position of the lead</td>
<td>x</td>
<td>x</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stimulation settings</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Implantation data</td>
<td>x</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patient status</td>
<td>x</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reimplantation</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adverse events</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Modification of the implanted system</td>
<td>x**</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table F.1: Data to be collected at each visit. Please note that the windows of the follow-up visits will follow the clinical practice of the study site. MC: multidisciplinary consultation; FI: fecal incontinence; *: only for the patients indicated for the stimulation test, but not enrolled in the study; **: only for the patients included in the Primary Population.
### ‘F.1.1 Screening Visit’ modified:

**Initial text:**
All the patients meeting all of the inclusion criteria, and none of the exclusion criteria, will be candidates for the stimulation test. The patients who will undergo a stimulation test will be included in the registry.

**Text modified:**
During a multidisciplinary consultation, all the patients indicated for the stimulation test and not opposed to the conduct of the study, and who meet all of the inclusion criteria and none of the exclusion criteria, will be included in the registry.

### ‘F.1.3 Initial (Baseline) Visit’ modified:

**Initial text:**
During the Initial (Baseline) Visit, which will take place after the 22nd day following the Screening visit, the following data will be collected [...]  

**Text modified:**
During the Initial (Baseline) Visit, after the confirmation of non-opposition of the patient to the conduct of this study, the following data will be collected [...]  

‘FIQL score’ replaced by ‘Score of the quality of life questionnaire FIQL’.

### ‘F.1.4 Test Visit’ modified:

**Initial text:**
At the end of the testing period, a multidisciplinary committee will meet to decide whether or not to proceed with the permanent implant. This decision will be based on the bowel diary and the overall impression of the patient regarding his/her possible improvement during the test.

**Text modified:**
The decision to proceed with the permanent implant will be based on the bowel diary and the overall impression of the patient regarding his/her possible improvement during the test.

### ‘F.1.6 Follow-up Visits at 1–3 Months, 3–6 Months and 1 Year (± 3 Months)’ modified:

**Initial title:**
F.1.6 Follow-up Visits at 1–3 Months, 3–6 Months and 1 Year (± 3 Months)  
**Modified title:**
F.1.6 Follow-up Visits at 1-3 Months, 4–8 Months and 9–15 Months

**Initial text:**
A bowel diary will be given to the patient before each visit, which will be completed during the last three weeks preceding the next follow-up visit. The quality of life questionnaire will be identical for each point.

**Text modified:**
A bowel diary will be given to the patient before each visit. This diary will be completed during the last three weeks preceding the next follow-up visit, and then given back to the patient at each visit. The quality of life questionnaire FIQL will be identical for each point.

### G LOGISTICAL ASPECTS

### ‘G.2.1 Initiation of the Study Sites’ modified:
<p>| | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Initial text:</strong></td>
<td>The study sites will be initiated by the Monitors or the Study Manager, who will have the responsibility of verifying that the site meets the minimum requirements to participate in this study.</td>
<td><strong>Text modified:</strong> The study sites will be initiated by the Monitors or the Study Manager, who will have the responsibility of verifying that the site meets the requirements to participate in this study.</td>
</tr>
<tr>
<td><strong>February 15, 2013</strong></td>
<td>**‘G.3.2.1 Site Initiation Visits’ modified:**<strong>Initial text:</strong> During this Site Initiation visit, the participation of this study site will be evaluated based on the following information: the starting date of the Interstim® therapy practice, the specialization of the clinicians involved, and the organization of the multidisciplinary consultation.</td>
<td><strong>Text modified:</strong> During this Site Initiation visit, the following information will be collected: starting date of the Interstim® therapy practice, the specialization of the clinicians involved, and the organization of the multidisciplinary consultation.</td>
</tr>
<tr>
<td><strong>I STUDY MANAGEMENT</strong></td>
<td><strong>Initial title:</strong> I.1 Study Members <strong>Modified title:</strong> I.1 Medtronic Personnel Involved in the Study</td>
<td><strong>Initial text:</strong></td>
</tr>
<tr>
<td>Position</td>
<td>Manager/Organization</td>
<td></td>
</tr>
<tr>
<td>----------------------------------------------</td>
<td>---------------------------------------------------------------------------------------</td>
<td></td>
</tr>
<tr>
<td>Study Sponsor</td>
<td>Medtronic France SAS. 27 Quai Alphonse Le Gallo</td>
<td>CS30001</td>
</tr>
<tr>
<td>Project Manager</td>
<td>Abdallah Aboulhia Medtronic International Trading Sarl Route du Molliou 31 CH-1131 Telochena Switzerland T.: +41 79557 9103 <a href="mailto:abdallah.aboulhia@medtronic.com">abdallah.aboulhia@medtronic.com</a></td>
<td></td>
</tr>
<tr>
<td>Study Manager</td>
<td>Valeria Burrone EMEA Regional Clinical Center Medtronic Clinical Research Institute piazza I. Montanelli 3 20099 Sesto (MI) Italy T.: +39 33552 95505 <a href="mailto:valeria.burrone@medtronic.com">valeria.burrone@medtronic.com</a></td>
<td></td>
</tr>
<tr>
<td>Data Management</td>
<td>Rohit Kulkarni EMEA International Clinical Operations Medtronic Clinical Research Institute Endegeosdomein 5 6229 GW Maastricht The Netherlands T.: +31 61319 0374 <a href="mailto:rohit.kulkarni@medtronic.com">rohit.kulkarni@medtronic.com</a></td>
<td></td>
</tr>
<tr>
<td>Installation and Maintenance of the Data Collection System</td>
<td>MedSharing</td>
<td></td>
</tr>
<tr>
<td>Statistics</td>
<td>Tiziana De Santo EMEA Regional Clinical Center Medtronic Clinical Research Institute VIA Lucrezio Caro 63</td>
<td>00193 Roma</td>
</tr>
<tr>
<td>Reimbursement</td>
<td>Alaine Topouchian Medtronic France SAS 27 Quai Alphonse Le Gallo</td>
<td>CS30001</td>
</tr>
<tr>
<td>Monitoring</td>
<td>Charlotte Pollet EMEA International Clinical Operations Medtronic Clinical Research Institute Endegeosdomein 5 6229 GW Maastricht The Netherlands T.: +41 (0) 79708 8145 <a href="mailto:charlotte.pollet@medtronic.com">charlotte.pollet@medtronic.com</a></td>
<td></td>
</tr>
</tbody>
</table>

Text modified:
The following table identifies the team members of the clinical study, including their function, contact information and organization. The composition of the team can be modified during the study. For this reason, regular updates will be sent to the study sites.
Moreover, Medtronic qualified personnel not directly involved in the conduct of the study may provide technical support during the test, the implant procedure or the device follow-up sections.

### J RISKS AND BENEFITS

#### 2 February 15, 2013

**‘1.1 Risks’ modified:**

*Initial text:*

All the devices used in this study were introduced on the market at the beginning of the study.

*Text modified:*

All the devices used in this study were commercialized before the start of the study.

### Appendix 1 - Patient Data Release Form and Non-Opposition to the Conduct of the Study Form

**Initial version:** version 1, November 14, 2012  
**Modified version:** version 2, January 11, 2013
This post-reimbursement study is “non-interventional”, which means that you will be under no obligation (no additional consultation, treatment, nor examination) and you will not receive any direct or immediate benefit. It does not affect in any way the quality and choice of the treatment that you will receive or have received. Your participation in the study will not exceed 16 months.

If you agree to participate, your physician will complete a questionnaire at each of your scheduled visits, meaning at the Initial visit of the Test visit (which will be named Baseline visit), and the Test visit. After these two visits, a committee of physicians will decide, based on your clinical data and your response to the therapy, if you are a suitable candidate for the permanent neurostimulator implant. If you are deemed a suitable candidate, you will receive a neurostimulator implant. In this case, your physician will complete a questionnaire on the implant procedure, as well as follow-up questionnaires: after 1–3 months, 3–6 months and 1 year (± 3 months).

If you are not deemed suitable for the implant, your data will only be collected by the physician 6 months after the decision not to give you an implant.

In all cases, the data collected will include your demographic data, your medical history, the safety and efficacy of the treatment, and possible adverse events.

This study involves the observation of patients followed according to the standard clinical practice. Therefore, this study would not take up any more of your time.

Moreover, the physician who will monitor your progress during the study will identify you using an identification code. For more information, see section Confidentiality and anonymity - a. For the clinical data collected during the study next page.

In addition, with your consent, your name and telephone numbers will be given to an organization located outside of the hospital that will have the responsibility of calling you three weeks before the next visit. The purpose of these phone calls will be to remind you of the date of the consultation and to bring the bowel diary and the quality of life questionnaire that will be given to you by the physician with you to the visit.

Text modified:

This study is “non-interventional”, which means that you will be under no obligation (no additional consultation, treatment, nor examination) and you will not receive any direct or immediate benefit. It does not affect in any way the quality and choice of the treatment that you will receive or have received. Your participation in the study will not exceed 16 months, unless the Haute Autorité de Santé (French National Authority for Health) requests an extension of the registry. In that case, you will be informed by your physician.

If you agree to participate, your physician will complete a questionnaire at each of your scheduled visits, meaning at the Initial visit and the Test visit. After these two visits, a committee of physicians will decide, based on your clinical data and your response during the test, if you are a suitable candidate for the permanent neurostimulator implant. If their decision is positive, you will receive a neurostimulator implant. Your physician will complete a questionnaire on the implant procedure, as well as follow-up questionnaires at 1–3 months, 4–8 months, and 9–15 months follow-up visits.

If their decision regarding the implant is negative, your data will only be collected by the physician during a visit which will take place 4–8 months after the decision not to give you an implant.

In all cases, the data collected will include your demographic data, your medical history, the safety and efficacy of the treatment, and possible adverse events.

In all cases, Medtronic qualified personnel may provide technical support during the test, the permanent implant procedure and the follow-up visits.

By signing this document, you accept that your name and telephone numbers will be given to an organization outside of the hospital (named Chiltern, headquarters at 37 bis rue de Villiers - 92200 Neuilly sur Seine - France) that will call you three weeks before each visit. The purpose of these phone calls will be to remind you of the date of the visit and to bring the bowel diary and the quality of life questionnaire that will be given to you by the physician with you to the visit.
be given to you by the physician with you to the visit. Your acceptance, or your refusal at any time, to participate in this study will be inconsequential for you and will not affect your medical care. Your participation in this study is voluntary and you can withdraw from the study at any time. The physician that will follow you during the study may also decide to remove you from the study at any time, and without your prior consent, for example, if you miss several consecutive visits. In this case, the physician will inform you of his/her decision and explain the reasons.

| 3 | May 30, 2014 | Study Sponsor: 
MEDTRONIC France SAS  
27 Quai Alphonse Le Gallo  
CS30001 – 92513 Boulogne-Billancourt Cedex - France  
replaced by the new study Sponsor:  
Medtronic International Trading Sàrl  
Route du Molliau 31  
CH-1131 Tolochenaz, Switzerland  
in the entire document. |
<p>| 3 | May 30, 2014 | The table included in the section I.1 The list of the Medtronic personnel involved in the study was updated. |</p>
<table>
<thead>
<tr>
<th>Position</th>
<th>Managers/Organization</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study Sponsor</td>
<td>Medtronic France SAS, 27 Quai Alphonse Le Gallo</td>
</tr>
<tr>
<td>Project Manager</td>
<td>Abdallah Alouihia Medtronic International Trading Sarl Route du Molliau 81 CH-1133 Tolochenaz Switzerland T: +41 79557 9167 <a href="mailto:a.aboulhia@medtronic.com">a.aboulhia@medtronic.com</a></td>
</tr>
<tr>
<td>Study Manager</td>
<td>Valeria Burrone EMEA Regional Clinical Center Medtronic Clinical Research Institute piazza I, Montanelli 3</td>
</tr>
<tr>
<td>Data Management</td>
<td>Rohit Kulkarni EMEA International Clinical Operations Medtronic Clinical Research Institute Endepoldomain 5</td>
</tr>
<tr>
<td>Installation and Maintenance of the</td>
<td>- MedSharing</td>
</tr>
<tr>
<td>Data Collection System</td>
<td></td>
</tr>
<tr>
<td>Statistics</td>
<td>Tiziana De Santo EMEA Regional Clinical Center Medtronic Clinical Research Institute Via Lucrario Caro 63</td>
</tr>
<tr>
<td>Reimbursement</td>
<td>Frédérique Debrocker Medtronic France SAS 27 Quai Alphonse Le Gallo</td>
</tr>
<tr>
<td>Monitoring</td>
<td>Charlotte Polly EMEA International Clinical Operations Medtronic Clinical Research Institute Endepoldomain 5</td>
</tr>
</tbody>
</table>

is replaced by table:
<table>
<thead>
<tr>
<th>Position</th>
<th>Manager/Organization</th>
</tr>
</thead>
</table>
| Study Sponsor                        | Medtronic International Trading Sàrl  
Route du Molliau 31  
CH-1131 Tolochenaz, Switzerland |
| Project Manager                      | Charlotte Pollet  
Medtronic International Trading Sàrl  
Route du Molliau 31 [CH-1131 Tolochenaz] Switzerland  
T.: +41 79 7098145  
E-mail: charlotte.pollet@medtronic.com |
| Study Manager                        | Claudia Campo  
EMEA Regional Clinical Center  
Medtronic Clinical Research Institute  
Piazza l. Montanelli 3 | 20099 Sesto SG (MI) Italy  
T.: +39 347 3265130  
E-mail: claudia.campo@medtronic.com |
| Data management                      | Virginie Gely  
EMEA International Clinical Operations  
Medtronic International Trading Sàrl  
Route du Molliau 31 [CH-1131 Tolochenaz] Switzerland  
T.: +41 21 803 8069  
E-mail: virgini.gely@medtronic.com |
| Installation and Maintenance of the Data Collection System | MedSharing |
| Statistics                            | Abdallah Abouihia  
Medtronic International Trading Sàrl  
Route du Molliau 31 [CH-1131 Tolochenaz] Switzerland  
T.: +41 79 557 9163  
E-mail: abdallah.abouihia@medtronic.com |
| Reimbursement                        | Béatrice Petzold  
Medtronic France SAS  
27 Quai Alphonse Le Gallo [CS30001] 92513 Boulogne-Billancourt Cedex [France]  
T.: +33 1 55381703  
E-mail: beatrice.petzold@medtronic.com |
| Monitoring                            | MCO CRAs  
EMEA International Clinical Operations  
Medtronic Clinical Research Institute  
Endepolandseim 5 [6229 GW Maastricht] The Netherlands |

3 May 30, 2014 The signature page was updated:
<table>
<thead>
<tr>
<th>Signature Page</th>
<th>Author: Abdallah Aboushe</th>
<th>Position</th>
<th>Date</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Clinical Management:</th>
<th>Valeria Burroni</th>
<th>Senior Clinical &amp; Research Specialist</th>
<th>Position</th>
<th>Date</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Medical Affairs:</th>
<th>Tanja Gabrecht</th>
<th>Medical Scientific Expert</th>
<th>Position</th>
<th>Date</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Quality:</th>
<th>Mark Harrison</th>
<th>Senior Clinical QA Specialist</th>
<th>Position</th>
<th>Date</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Regulatory Affairs:</th>
<th>Cécile Fourot</th>
<th>Regulatory Affairs Manager</th>
<th>Position</th>
<th>Date</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Legal Affairs:</th>
<th>Julie Marot</th>
<th>Senior Legal Manager</th>
<th>Position</th>
<th>Date</th>
</tr>
</thead>
</table>

is replaced by:
The “Patient Data Release Form” and the “Non-opposition to the Conduct of the Study Form” were updated with a new version number and date (version 3, May 30, 2014) and with a new Sponsor.

Table B.1 was updated with:

- Stimulation cable with minihook – Model 3575
- Twist-lock cable – Model 3576
- Patient Programmer - Model 3537

The duration of the inclusion period and the duration of the study were modified to 46 months and 60 months, respectively, in the entire document.
TABLE OF CONTENTS

A. SYNOPSIS.......................................................................................................................... 21

B. BACKGROUND.................................................................................................................. 25
   B.1 Fecal incontinence.......................................................................................................... 25
      B.1.1 Epidemiology of Fecal Incontinence ................................................................. 25
      B.1.2 Etiologies ............................................................................................................ 25
      B.1.3. Treatments ......................................................................................................... 26
   B.2 Role of Sacral Neuromodulation in the Treatment of Fecal Incontinence.............. 27
      B.2.1 Description of the Devices .................................................................................. 27
      B.2.2 Indications .......................................................................................................... 28
      B.2.3 Treatment Follow-up ......................................................................................... 29

C. STUDY DESIGN.................................................................................................................. 30
   C.1 Study Rationale and Objectives................................................................................... 30
      C.1.1 Primary Objective ............................................................................................... 30
      C.1.2 Secondary Objectives ........................................................................................ 30
   C.2 Outcome Measures....................................................................................................... 32
      C.2.1 Primary Outcome Measure ................................................................................ 32
      C.2.2 Secondary Outcome Measures ......................................................................... 33
   C.3 Study Population.......................................................................................................... 35
   C.4 Study Design................................................................................................................ 37
   C.5 Use of the Control........................................................................................................ 37
   C.6 Study Hypothesis and Statistical Analysis.................................................................. 37
   C.7 Sample Size Requirement........................................................................................... 38
      C.7.1 Interim Analysis .................................................................................................... 38
   C.8 Number of Study Sites and Study Duration............................................................... 39

D. SELECTION OF THE PATIENTS........................................................................................ 40
   D.1 Inclusion Criteria.......................................................................................................... 40
   D.2 Exclusion Criteria.......................................................................................................... 40

E. STUDY PREPARATION...................................................................................................... 41
   E.1 Selection of the Investigators and Study Sites............................................................. 41
      E.1.1 Clinical Study Agreement .................................................................................... 41
      E.1.2 Curriculum Vitae ................................................................................................. 41
   E.2 Regulatory Approvals................................................................................................... 42
      E.2.1 Approval of the Regulatory Authorities ............................................................... 42
      E.2.2 Patient Data Release Form and Non-opposition to the Conduct of the Study Form 43
      E.2.3 Data Security ....................................................................................................... 43
   E.3 Regulations and Good Practices in Epidemiology....................................................... 44
H.1.2 Follow-up Data

H.2 Publications

H.2.1 Reports

H.2.2 Publications and Presentation of the Results

I. STUDY MANAGEMENT

I.1 Medtronic Personnel Involved in the Study

I.2 Advisory Committees

I.2.1 Scientific Committee

I.2.2 Other Advisory Committees

I.3 Reports and Documents Management

I.3.1 Retention of the Documents at the Sites

I.3.2 Responsibilities of the Investigators

I.3.3 Documents Archived by the Sponsor

I.3.4 Responsibilities of the Sponsor

I.4 Miscellaneous

I.4.1 Insurance

I.4.2 Data Confidentiality

J. RISKS AND BENEFITS

J.1 Risks

J.2 Possible Benefits

K. REFERENCES

L. APPENDICES

Appendix 1 Patient Data Release Form and Non-opposition to the Conduct of the Study

Appendix 2 List of the Medtronic Personnel Involved in the Study

Appendix 3 List of the Sites Participating in the Study

Appendix 4 Example of Case Report Forms

Appendix 5 Copy of the Clinical Trial Agreement

M. List of Abbreviations and Acronyms
## A. SYNOPSIS

<table>
<thead>
<tr>
<th>Study Title</th>
<th>Post-Approval Follow-up Study on Sacral Neuromodulation for the Treatment of Fecal Incontinence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sponsor</td>
<td>Medtronic International Trading Sàrl&lt;br&gt;Route du Molliau 31&lt;br&gt;CH-1131 Tolochenaz, Switzerland</td>
</tr>
<tr>
<td>Product Name</td>
<td>Medtronic Interstim®, implantable sacral nerve neurostimulation system (S3) (Models 3023 et 3058) and any future system upgrades.</td>
</tr>
<tr>
<td>Justification</td>
<td>Study conducted at the request of the Haute Autorité de Santé (French National Authority for Health).</td>
</tr>
<tr>
<td>Study Design</td>
<td>Observational, prospective, multi-center, non-randomized, non-controlled longitudinal study with a follow-up following routine clinical practices i.e. follow-up visits at 1–3 months, 4–8 months and 9–15 months after device implant.</td>
</tr>
<tr>
<td>Objectives</td>
<td>Evaluate the efficacy of sacral neuromodulation, the rates of definitive explant, revision and replacements, the adverse events, the quality of life, and the practices.</td>
</tr>
<tr>
<td>Outcome Measures</td>
<td><strong>Primary Outcome Measure</strong>&lt;br&gt;The proportion of the patients presenting a reduction of at least 50% in the number of leaks per week at the 4–8 months follow-up visit, compared to baseline, and having no serious adverse event or serious adverse device effect (short-term serious adverse events or short-term serious adverse device effects are excluded in this context), among all patients implanted at the end of the test period.&lt;br&gt;&lt;br&gt;<strong>Secondary Outcome Measures</strong>&lt;br&gt;- The proportion of the patients presenting a reduction of at least 50%, compared to the baseline value (measured at the Initial Visit), in the average number of:&lt;br&gt;  o Bowel movements per week;&lt;br&gt;  o Urgencies per week;</td>
</tr>
</tbody>
</table>
- The increase in retention period over time;
- The proportion of the patients presenting at least one complication;
- The reduction in severity of the fecal incontinence using the Wexner score;
- The improvement in quality of life based on the FIQL score;
- The satisfaction level of the patients;
- The evaluation of the practices.

### Eligibility Criteria

#### Inclusion Criteria

- A patient not opposed to the conduct of the study and who signed the “Patient Data Release Form”;
- A patient who can understand the information provided by the physician regarding the collection and publication of his/her personal information, and who may object to this collection and publication.
- A patient ≥18 years-old, suffering from fecal incontinence;
- A patient indicated for a sacral neuromodulation test for InterStim®.

#### Exclusion Criteria

- Replacement of the neuromodulator of patients who were implanted before the inclusion period and did not undergo a stimulation test
- A patient who refuses, or objects to, the collection and publication of his/her personal information.

### Study Population/Treatment

Approximately 286 patients will be included in the registry. All the sites qualified to treat fecal incontinence by sacral neuromodulation will be contacted. The study sites will have to invite all the patients having a primo-implantation or replacement (reimplantation) to participate in the study, in the latter case if, and only if, a test is performed during the inclusion period.

### Sample Size and Statistical Analysis

#### Sample Size

With a conservative hypothesis of 50% of the patients achieving a reduction of at least 50% in the number of leaks per week, compared to baseline, 200 patients must be implanted in order to estimate a two-sided 95% confidence interval with a precision of 7 decimals.
Considering a hypothesis of 30% of the patients tested, but not implanted or lost to follow-up, approximately 286 patients will be included in the registry.

**Statistical Analyses:**

The descriptive analysis of the qualitative and ordinal variables will include the number and rate of each modality with the corresponding 95% confidence interval. The descriptive analysis of the quantitative variables will include the mean, standard deviation, confidence interval and median of the extreme values.

Survival analyses will describe the distribution and duration of the benefits resulting from the therapy.

Repeated measures ANOVA will describe the evolution over time of the severity of fecal incontinence, the quality of life and patient satisfaction.

The survival models and linear models will be adjusted using the demographic data and other prognostic factors of fecal incontinence.

<table>
<thead>
<tr>
<th>Study Population/Treatment</th>
<th>Two study populations will be defined:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>• The Primary Population including the patients tested and implanted with a sacral nerve neuromodulator for the treatment of fecal incontinence (Interstim®).</td>
</tr>
<tr>
<td></td>
<td>• The Secondary Population including the patients tested and not implanted.</td>
</tr>
</tbody>
</table>

All the analyses will first be conducted on the Primary Population. Afterward, a descriptive analysis of the primary outcome measure and secondary outcome measures will be conducted for the Secondary Population between 4–8 months of follow-up.

| Study Duration | The total study duration is estimated at approximately 60 months, with an inclusion period of 46 months. The entire follow-up period of each patient will not exceed 15 months after the decision of the Committee on the permanent implant. |

<table>
<thead>
<tr>
<th>Data Collected</th>
<th>Data collected during the Inclusion Visit:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Sociodemographic data (age, gender), characteristics of the disease (etiology of the incontinence, related disorders), medical and surgical history, previous treatments of fecal incontinence, clinical assessment (bowel diary, Wexner scores and quality of life questionnaire FIQL (completed by the patient)), function assessment (anorectal manometry, endoanal ultrasound, markers transit), test</td>
</tr>
</tbody>
</table>
and implantation data, early complications.

**Follow-up Data:**

Patient satisfaction, clinical assessment (bowel diary, Wexner scores and quality of life questionnaire FIQL (completed by the patient)), function assessment (anorectal manometry, markers transit), the need to reprogram the neuromodulator, and complications during the follow-up period.

**Data collection**

The data will be collected using the electronic Case Report Form (eCRF). The data entered will be managed continuously.
B BACKGROUND

B.1 Fecal Incontinence

B.1.1 Epidemiology of Fecal Incontinence

Anus-related fecal incontinence leads to the inability to prevent gas and/or stool leakage. This is a common condition, but it remains taboo. These problems can occur throughout life, but their rate tends to increase with aging. Fecal incontinence may be associated with urinary incontinence. The estimated rate of fecal incontinence depends on the definition criteria used (namely whether or not to include cases of flatal incontinence only) and the investigation methods (incontinence reported by the patient or the physician).

A survey performed in 1989 on a sample size representative of the French population estimated that 11% of individuals over 45 years-old suffer from fecal incontinence. In December 2006, a mail survey was conducted in Rhône-Alpes in collaboration with the Regional Health Observatory (RHO). A total of 2,800 individuals were selected at random from the electoral lists. Among the 807 questionnaires returned, the prevalence of fecal incontinence was 5.2%. Comparable percentages (2.2–7.1%) were reported in Anglo-Saxon studies conducted on the general population.

Based on these data, about 2 million individuals would suffer from fecal incontinence in France. Fecal incontinence affects women more often for anatomical and physiological reasons (childbirth), but may also affect men (medical conditions or complications from anorectal surgery).\(^{3,4}\)

B.1.2 Etiologies

There are multiple causes:

- **For women, childbirth is among the main causes.** The perineal nerves controlling the sphincter may be damaged. In some cases, anal fissures can be diagnosed immediately after childbirth. But in most cases, these skin lesions are detected much later in life.

- **Proctological surgery** (anal fissure, hemorrhoids, fistulas and abscesses) may damage the anal sphincter and cause a tear. Anal and perianal infections may also cause lesions in the anal sphincter, leading to fecal incontinence.

- **The diseases affecting the nervous system** which, consequently, disrupt the communications between the brain and the vesical or anal sphincter (e.g. stroke, multiple sclerosis, Parkinson’s disease or spinal cord injury).
• The adverse events of certain medications (e.g. antidepressants, sedatives, diuretics or muscle relaxants).
• Congenital malformations (spina bifida, imperforate anus, etc.).
• Weakening of the pelvic floor muscles which may occur during menopause or as part of the natural ageing process.
• Chronic diarrhea may often exacerbate the symptoms of fecal incontinence.

Fecal incontinence is a serious handicap that considerably reduces the quality of life of the affected patients. Unfortunately, this disease is considered degrading and shameful by the patients, and is often perceived as inevitable. Furthermore, fecal incontinence is rarely mentioned spontaneously by the patients during medical treatments.\textsuperscript{3,4}

B.1.3 Treatments

The management of fecal incontinence requires a multidisciplinary team and modern technical resources.

After careful questioning, a complete physical examination, and possibly further examinations, a treatment can be suggested.

For cases of moderate incontinence, a pharmaceutical treatment may be suggested (medications slowing down intestinal transit, dietary recommendations).

In some cases, rehabilitation using the biofeedback method could be very useful. In fact, the force of voluntary contraction of the anus may be significantly increased using this rehabilitation method. However, the efficiency of this approach requires specific material and a therapist specialized in perianal rehabilitation.

Finally, a surgical procedure is sometimes necessary.

In summary, the different treatment modalities for fecal incontinence are the following:

  ✓ diet modifications;
  ✓ medications restoring normal intestinal transit;
  ✓ perianal rehabilitation using the biofeedback method;
  ✓ surgery;
  ✓ neuromodulation of the sacral nerve roots.\textsuperscript{13,15}
B.2 Role of Sacral Neuromodulation in the Treatment of Fecal Incontinence

B.2.1 Description of the Devices

The Interstim® therapy uses the following products available on the market:

<table>
<thead>
<tr>
<th>Components</th>
<th>References</th>
<th>Intended use</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disposable parts for individual use</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Interstim®</td>
<td>3023, 3058</td>
<td>Autonomous and programmable sacral nerve neuromodulator</td>
</tr>
<tr>
<td>Interstim II®</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Quadripolar leads</td>
<td>3093, 3889</td>
<td>For the stimulation test and the permanent implant</td>
</tr>
<tr>
<td>Extension</td>
<td>3095</td>
<td>Connects the lead to the neuromodulator (Interstim® Model 3023 only)</td>
</tr>
<tr>
<td>Cables</td>
<td>3575, 3576</td>
<td>Stimulation cable with minihook</td>
</tr>
<tr>
<td>Introducer kit</td>
<td>3550-18</td>
<td>For the insertion of the percutaneous lead</td>
</tr>
<tr>
<td>Patient programmer</td>
<td>3037, 3537</td>
<td>Adjustment of the stimulation intensity by the patient,</td>
</tr>
<tr>
<td></td>
<td></td>
<td>within the limits programmed by the physician.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Allows the physicians to program the settings of the external neurostimulator.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Allows the patients to turn on/off the device and to adjust the stimulation intensity.</td>
</tr>
<tr>
<td>Parts for individual use</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test stimulator</td>
<td>3625, 3531</td>
<td>Temporary stimulator test stimulation before the definitive implant</td>
</tr>
<tr>
<td>Parts not for individual use</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Programmer N’Vision for</td>
<td>8840</td>
<td>Adjustment of the stimulation settings of the neuromodulator</td>
</tr>
<tr>
<td>physicians</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Software used with the</td>
<td>8870</td>
<td>Software used with the physician’s programmer</td>
</tr>
<tr>
<td>reference console</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table B.1: Devices used in the study.

For more information on how to use the device, the indications and contraindications, the complications (complete list), the precautions and potential adverse events, refer to the User Manual provided with the device.¹

The registry is designed to include new components of the device as soon as they become available and commercialized for the treatment of fecal incontinence.
B.2.2 Indications

Neuromodulation constitutes a comfortable minimally-invasive treatment method for fecal incontinence, tailored to the specific needs of each patient. Furthermore, this therapy can address urinary and fecal incontinence simultaneously when the two conditions are related, because neuromodulation of the sacral nerve roots has the advantage to treat the dysfunctions of the entire pelvic floor.\textsuperscript{5–8,10}

The Interstim® device, created by Medtronic, treats urinary and fecal incontinence through sacral neuromodulation. On December 8, 2009, the Commission nationale d'évaluation des dispositifs médicaux et des technologies de santé (CNEDIMTS, Medical Device and Health Technology Evaluation Committee) issued an opinion indicating an improvement of the level IV expected outcome, compared to the standard therapeutic approach.\textsuperscript{2}

Sacral neuromodulation is indicated for cases of fecal incontinence refractory to conservative therapies, but with a functional anal sphincter, defined as follows:

- Intact sphincter (no lesion or after sphincter repair)
- Altered sphincter, if the size of the lesion does not justify sphincter repair. (opinion of the CNEDIMTS, dated December 8, 2009)

Treatment by sacral neuromodulation is contraindicated under certain conditions: anorectal or pelvic malformations, sequelae of rectal resection, extensive degradation of the sphincter, sequelae of radiation proctitis and chronic inflammatory diseases, neurological disease or systemic diseases (multiple sclerosis, scleroderma, paraplegia...). A careful psychological assessment is also important.

This opinion also stated that the decision to perform the implantation of an Interstim® device must be made during a multidisciplinary consultation combining the following specializations: digestive surgery targeting the colorectum, gastro-enterology with proficiency in coloproctology, functional assessment of the digestive and pelvic tissues, and specialized radiology. The opinion of a psychiatrist must be solicited.

During the decision-making process, the evaluations cover the medical history, the clinical assessment including a bowel diary of three weeks and the fecal incontinence scores (Wexner + FIQL), and a functional assessment based at least on an anorectal manometry. An endoanal ultrasound and dynamic imaging of the anorectal and pelvic statics must be performed, if necessary.

B.2.2.1 Neurostimulation Test

The neurostimulation test will be conducted according to the local practices of the study site.
During this visit, the investigator will determine whether the neurostimulation is positive or negative, according to the standard protocol used at the study site to evaluate the success of a neurostimulation test.

B.2.2.2 Permanent Implant

The decision to proceed with the permanent implant must be made during a multidisciplinary consultation and based on the bowel diary and overall impression of the patient regarding his/her possible improvement during the test.

B.2.3 Treatment Follow-up

The stimulation settings of the system are programmed by the practitioner or treating personnel properly trained on the use of the N'Vision programmer. The patient’s remote control allows the patient to adjust the stimulation intensity within the limits programmed by the physician (choice of two intensity/frequency programs defined by the physician) and to turn on/off the neuromodulator.
C STUDY DESIGN

C.1 Study Rationale and Objectives

At the request of the Haute Autorité de Santé (HAS, French National Authority for Health (opinion of the CNEDIMTS of December 8, 2009), Medtronic must conduct an observational study on the use of the Interstim® device for the indication of fecal incontinence. The goal is to set up an exhaustive registry of all the patients who benefited from an Interstim® stimulator for the treatment of fecal incontinence, in order to evaluate the practices, the efficacy of sacral neuromodulation, the rates of definitive explant, revision and replacement, the complications and adverse events.

C.1.1 Primary Objective

Based on the opinion of the CNEDIMTS of December 8, 2009, the test is considered positive if the number of episodes of incontinence is reduced by at least 50%, as measured in a bowel diary completed for at least 21 days.

The primary objective is to evaluate the proportion of the patients who presented a reduction of at least 50% in the number of episodes of incontinence, compared to baseline, as indicated in a bowel diary completed for at least 21 days, and who did not have any serious adverse event or serious adverse device effect (short-term serious adverse events or short-term serious adverse device effects are excluded in this context), among all the patients who received an Interstim® stimulator for the treatment of fecal incontinence.

C.1.2 Secondary Objectives

C.1.2.1 Average Number of Bowel Movements per Week

Evaluate the percentage of the patients who exhibited a reduction of at least 50% in the number of bowel movements per week, compared to baseline, as indicated in a bowel diary completed for 21 days, among all the patients who received an Interstim® stimulator for the treatment of fecal incontinence.

C.1.2.2 Average Number of Urgencies per Week

Evaluate the percentage of the patients who exhibited a reduction of at least 50% in the number of urgencies per week, compared to baseline, as indicated in a bowel diary completed for 21 days, among all the patients who received an Interstim® stimulator for the treatment of fecal incontinence.
C.1.2.3 Retention Period over Time

Evaluate the proportion of the patients who exhibited a significant increase in retention period.

An increase in the retention period is important for the quality of life of patients suffering from fecal incontinence, and the sacral neuromodulation provided by the Interstim® device usually has a favorable impact on this aspect of the pathology.

C.1.2.4 Complications and Adverse Events

Evaluate the percentage of the complications and adverse events linked to the Interstim® device, the implantation procedure and/or the concomitant treatments.

All adverse events will be documented and analyzed to evaluate the long-term safety of sacral neuromodulation for the treatment of fecal incontinence.

C.1.2.5 Severity of Fecal Incontinence

Evaluate the reduction in the severity of fecal incontinence of the patients who received an Interstim® stimulator for the indication of fecal incontinence, based on the Wexner score.

The Wexner score varies between 0 and 20, where 20 indicates complete incontinence. The reduction in the severity of fecal incontinence will be calculated as the difference between the score obtained before implantation at the Baseline visit and the score obtained at the Follow-up visit.

C.1.2.6 Quality of Life

Evaluate the improvement in quality of life of the patients who received an Interstim® stimulator for the indication of fecal incontinence, based on the FIQL score.

Fecal incontinence has a very negative impact on the quality of life of the patients. This study, therefore, will evaluate the efficacy of sacral neuromodulation for the improvement of the quality of life of the patients implanted.

The FIQL questionnaire contains 29 items grouped into four dimensions: lifestyle (10 items) behavior/coping (9 items), depression (7 items) and self-perception/embarrassment (3 items).

Each item is given a grade of 1 to 4 (1 corresponding to the worst situation) to calculate the score of each dimension.

The difference between the follow-up value and the baseline value will be calculated for the score of each dimension and for the total score.
C.1.2.7 Patient Satisfaction

Evaluate the satisfaction of the patients implanted with the Interstim® stimulator for the treatment of fecal incontinence on a scale of -5 to +5, with -5 if the patient is not satisfied at all and +5 if the patient is very satisfied of the Interstim® therapy. The decision to proceed with the permanent implant is based on the overall impression of the patient regarding his/her improvement during the testing period.

C.1.2.8 Evaluation of the Current Practices and Implantation Techniques

Describe the duration of the neuromodulation test, the standard implantation techniques, how to use the device, and the modifications of the stimulation settings.

C.1.2.9 Description of the Population of Patients Tested and Not Implanted

Evaluate the patients tested and not implanted at the 4–8 months follow-up visit, with respect to the sociodemographic data, the characteristics of the disease, the bowel diary, the Wexner scores and the quality of life questionnaire FIQL.

C.2 Outcome Measures

C.2.1 Primary Outcome Measure

The primary outcome measure is the proportion of the patients presenting a reduction of at least 50% in the number of leaks per week at the 4–8 months follow-up visit, compared to baseline, as measured in a bowel diary completed for 21 days, and who did not have any serious adverse event or serious adverse device effect (short-term serious adverse events or short-term serious adverse device effects are excluded in this context), among all the patients implanted at the end of the testing period.

Other outcome measures are used to evaluate the treatment of the fecal incontinence, including the number of leaks per week, the Wexner score and the FIQL score. However, all experts agree that they should be part of the secondary objectives. It is important to mention that the Wexner score does not enable quantifying the stool leaks of patients with severe incontinence. The relative difference will be calculated with respect to the baseline value obtained before the test, and will be expressed as a percentage.

The average number of leaks per week will be calculated using a bowel diary completed for a period of 21 days.
For example, a patient suffering from 20 leaks per week at baseline, and then showing a decrease to 5 leaks per week, will present a relative difference of \(\frac{20 - 5}{20}\) equal to 75%. If the leaks stop completely, the relative difference is 100%. If there is no improvement, the relative difference is 0%.

The test will be considered positive for a relative difference of at least 50%.

Therefore, the variable corresponding to the primary outcome measure is binary, with values of 0 (failure) or 1 (success), according to the patients:

- 0 corresponds to a relative difference inferior to 50% (reduction of <50% of the number of leaks)
- 1 corresponds to a relative difference superior or equal to 50% (reduction of ≥50% of the number of leaks)

The rate of « 1 » values corresponds to the rate of success.

### C.2.2 Secondary Outcome Measures

#### C.2.2.1 Relative Difference in Number of Leaks per Week at the 9–15 months Follow-up Visit

The proportion of the patients presenting a reduction of at least 50% in the number of leaks per week at the 9–15 months follow-up visit, compared to baseline, as indicated in a bowel diary completed for 21 days, among all the patients implanted at the end of the testing period.

The relative difference will be calculated with respect to the baseline value obtained before the test, and will be expressed as a percentage.

#### C.2.2.2 Relative Difference in Number of Bowel Movements per Week

The proportion of the patients presenting a reduction of at least 50% in the number of bowel movements per week at the 4–8 months and 9–15 months follow-up visits, compared to baseline, as indicated in a bowel diary completed for 21 days, among all the patients implanted at the end of the testing period.

The relative difference will be calculated with respect to the baseline value obtained before the test, and will be expressed as a percentage.

#### C.2.2.3 Relative Difference in the Number of Urgencies per Week

The proportion of the patients presenting a reduction of at least 50% in the number of urgencies per week at the 4–8 months and 9–15 months follow-up visits, compared to baseline. This reduction will be calculated using a bowel diary completed for 21 days, compared to baseline, among all the patients implanted at the end of the testing period.
The relative difference will be calculated with respect to the baseline value obtained before the test, and will be expressed as a percentage.

**C.2.2.4 Retention Period over Time**

There is currently no specific definition of a significant increase in retention period. It is difficult for the patients to quantify the retention period of each bowel movement, and thus, to estimate accurately the mean retention period over 21 days, before and after the test. To calculate the duration of the retention period, the patients would need to time each period preceding a bowel movement.

The following question will be asked to the patients:

*Do you consider that your retention period has increased or significantly improved? Yes/No*

The proportion of the patients who reported a significant improvement in retention period at the follow-up visits is calculated.

**C.2.2.5 Complications and Adverse Events**

The investigators have the responsibility of recording and documenting all the adverse events occurring after the patient is included in the registry. All the types of adverse events are collected and described (see section F.5 Adverse Events).

The adverse events will be presented with the number and proportion of the patients for each type of adverse event.

The total number of events and the number of patients exhibiting at least one adverse event, considering their severity and the relation to the device will allow quantifying the incidence of the adverse events.

**C.2.2.6 Severity of Fecal Incontinence**

The reduction in the severity of fecal incontinence corresponds to the difference in Wexner scores calculated at the Baseline (or Initial) visit and the Follow-up visit.

**C.2.2.7 Quality of Life**

The improvement in quality of life of the patients receiving the Interstim® therapy corresponds to the difference in FIQL scores calculated at the Baseline visit and the Follow-up visit, for the scores of all four dimensions and the total score.
C.2.2.8 Patient Satisfaction

The level of satisfaction of the patients will be evaluated during the testing phase and at the follow-up visits.
We determine the percentage of satisfied patients at each follow-up visit, and the changes in this percentage after 4–8 and 9–15 months of stimulation.

C.2.2.9 Evaluation of the Current Practices and Implantation Techniques

The duration of the test will be described. For each patient, the duration of the test will be calculated from the difference between the start date and end date of the test.
The type of lead, the position of the lead, and the model of neurostimulator implanted will be described.
The specialization of the operating physician and the specializations represented during the multidisciplinary consultation will be indicated.

C.3 Study Population

Based on the opinion of the CNEDIMTS of December 8, 2009, the expected number of patients is estimated to be less than 500 patients per year. However, given the progressive implementation of this activity at the sites, and that the Interstim® therapy has only been available for a few years for fecal incontinence, between 200 and 300 patients are expected to participate in this study.
Once the non-opposition of the patient to the conduct of this study has been obtained through the signature of the “Patient Data Release Form”, and the inclusion and exclusion criteria have been validated, the patient will be included in the study and evaluated for the stimulation test. If the test is positive, the patient will be included in the Primary Population (PP); and if the test is negative, the patient will be included in the Secondary Population (SP), as indicated in the following flow diagram (Figure C.1).
Multidisciplinary consultation meeting (MCM): Is the patient admissible for the test?

yes

Screening visit Can the patient be included in the registry? no

yes

Baseline visit

Stimulation test negative test

Follow-up visit at 6 months

SECONDARY POPULATION

Permanent Implantation

Follow-up visits: 1–3 months, 4–8 months, 9–15 months, according to the clinical practice of the study site

PRIMARY POPULATION

Figure C.1: Flow diagram showing the two study populations.
C.4 Study Design

This is an observational, prospective, multi-center, longitudinal study not randomized and not placebo-controlled, including standard follow-up visits per the sites’ routine practices. For each patient, data will be collected at the inclusion, the Baseline (or Initial) visit and the Test visit. For the patients who will receive a permanent implant, data will also be collected at the Implantation visit, and the Follow-up visit taking place 1–3 months after the implantation, 4–8 months after the implantation and 9–15 months after the implantation. For the patients tested and not implanted, follow-up data will only be collected during a visit taking place 4–8 months after the multidisciplinary consultation.

C.5 Use of Control

This study is not controlled.

C.6 Study Hypothesis and Statistical Analysis

Descriptive analyses will be performed and 95% confidence intervals will be calculated for the clinically-relevant variables, as described in a separate Statistical Analysis Plan (SAP). All the analyses will be performed on all the patients included in the registry. The primary analysis will be conducted on the Primary Population, whereas secondary and exploratory analyses will be conducted on the Primary Population and Secondary Population, as described in details in the Statistical Analysis Plan. A patient will be included in the registry if all of the inclusion criteria, and none of the exclusion criteria are met, and the stimulation test is conducted for the implantation of the Interstim® device. The qualitative variables will be expressed as frequencies of the modalities with the corresponding bilateral 95% confidence intervals. The quantitative variables will be expressed as the mean, standard deviation, minimum, maximum, median, quartiles, and number of missing data. The percentages of patients experiencing an improvement in the number of leaks, bowel movements and urgencies will be compiled over time in the survival curve using actuarial methods.
Additional Analyses:

All the analyses could be stratified per site if the number of patients included at each site is sufficient to support this type of analyses. However, it is important to mention that the protocol does not currently involve a comparison of the sites.

For exploratory purposes, the evaluation criteria used to decide whether or not to proceed with the permanent implant could be analyzed by adjusting the main characteristics of the patients, such as age, number of years of the illness, main cause of the fecal incontinence, type of fecal incontinence, baseline clinical assessment data and gender.

All the analyses will be performed using the SAS statistical software for Windows version 9.1.

C.7 Sample Size Requirement

With a conservative hypothesis of 50% of the patients achieving a reduction of at least 50% in the number of leaks per week, compared to baseline,\textsuperscript{13, 14, 15, 16} 200 patients must be implanted in order to estimate a two-sided 95% confidence interval with a precision of 7 decimals.

For example, if the success rate observed with a small sample size of 200 patients is 70%, there is more than a 95% chance that the probability of success (for a very large population) would fall within the interval [63%, 77%].

Considering a hypothesis of 30% of the patients tested, but not implanted or lost to follow-up, approximately 286 patients will be included in the registry.

This is an exhaustive registry, and all the data of the patients tested will be collected, unless the patient refuses. The follow-up period should not exceed 15 months. However, the registry could be extended based on a discussion planned with the HAS in December 2013.

C.7.1 Interim Analysis

The objective of the study is to assess the long-term efficacy and safety of Interstim\textsuperscript{®}. Details on the interim analyses that will be performed will be provided in a separate Statistical Analysis Plan. The results of the interim analyses will be presented and published.
C.8 Number of Study Sites and Study Duration

All the sites offering the Interstim® therapy for fecal incontinence will be contacted to participate in the study. However, the Sponsor may conduct visits to sites before the initiation of the study to verify that they meet the minimum requirements (the clinicians understand the Clinical Investigation Plan and the procedures to complete the CRFs and reports, the Clinical Study Agreement between the site/clinician and the Sponsor has been signed by both parties, the site practices or started to practice the therapy, the site possesses the infrastructures and services needed to ensure compliance with the study procedures, etc.). For more information, see section G.3.2.1 Site Initiation Visits.

Given the fact that the reimbursement of this technology only started recently, the total number of sites that will practice this therapy is currently unknown. New sites might be included throughout the inclusion period, depending on the date at which they will start this practice.

The total duration of the study is determined by the inclusion period of 286 patients.

- Inclusion period of 286 patients: 46 months
- Follow-up period of each patient: 9–15 months
- Total duration of the study: 60 months
D SELECTION OF PATIENTS

This study is conducted on all the patients who underwent primo-implantation of an Interstim® device for fecal incontinence, or those who received a replacement (reimplantation) if, and only if, a test is performed during the inclusion period.

Before a patient is included in the study, the clinician will need to explain the study to the patient and confirm the non-opposition of the patient to the conduct of this study.

All the patients tested for a possible implantation will be included. If the test is negative, a 4–8 month evaluation is sufficient.

Section D.1 Inclusion Criteria

- A patient not opposed to the conduct of the study who signed the “Patient Data Release Form”;
- A patient who can understand the information provided by the physician regarding the collection and publication of his/her personal information, and who may object to this collection and publication.
- A patient ≥18 years-old, suffering from fecal incontinence;
- A patient indicated for a sacral neuromodulation test for InterStim®.

D.2 Exclusion Criteria

- Replacement of the neuromodulator of patients who were implanted before the inclusion period and did not undergo a new stimulation test;
- A patient who refuses, or objects to, the collection and publication of his/her personal information.
E STUDY PREPARATION

E.1 Selection of the Investigators and Study Sites

All the sites practicing the Interstim® therapy for fecal incontinence will be contacted to participate in the study, in order to obtain a sample size representative of all the patients treated in France.

Before activating a site, the Sponsor will have the responsibility of verifying that the site meets the following conditions:

- Clinical Study Agreement between the site/clinician and the Sponsor;
- Documents of non-opposition of the patient to the conduct of this study (approved versions of the Patient Data Release Form and Non-Opposition to the Conduct of the Study Form) that will be given to the patients (ISO 14155 8.2.2);
- Recent Curriculum Vitae of the investigators (signed and dated);
- Site Training Form signed by all members of the medical team of the site, which certifies that they have received the training on the study;
- Delegated Task List (DTL) containing a list of the clinical team members, the tasks delegated to each of member, and the authorization of the Principal Investigator;
- Report on the Site Initiation Visit.

E.1.1 Clinical Study Agreement

A Clinical Study Agreement will be signed by the site/clinician and the Sponsor before the start of the study at the site. A copy of the agreement will be maintained by the Sponsor and another will be kept by the site/clinician. By singing this agreement, the investigator/site will approve the Clinical Investigation Plan and its future amendments.

E.1.2 Curriculum Vitae

Before site activation, the investigators must provide their recent Curriculum Vitae signed and dated. They must describe their qualifications and year of completion, as well as their current position. The CV must have been signed less than 3 years before the activation of the site.
E.2 Regulatory Approvals

E.2.1 Approval of the Regulatory Authorities

This study will be evaluated by the following committees:

- Comité consultatif sur le traitement de l’information en matière de recherche dans le domaine de la santé (CCTIRS, Advisory Committee on the Treatment of Information related to health research);
- Commission nationale de l’informatique et des libertés (CNIL, National Commission on Informatics and Liberty);
- Conseil National de l’Ordre des Médecins (CNOM, French National Medical Council).

E.2.1.1 CCTIRS and CNIL

The patients will be identified by a site number and a patient number. The link between the site and patient numbers and the identity of the patient will be kept at the sites. To support the longitudinal follow-up and minimize the number of patients lost to follow-up, the study uses a call center (provisioned by the CRO Chiltern) to call the patients in order to remind them the date of their next follow-up visit and to complete the bowel diary and FIQL questionnaire. The phone calls will be made three weeks before the scheduled date of the follow-up visit.

To do this, the sites will need to give to the CRO the personal identifiers and telephone numbers of the patients included in the study. These identification data will be used only for the purpose of reminders. They will be entered in a secure database, other than the clinical database, to which the Sponsor will not have access. Furthermore, these data will be destroyed after they have been used by the CRO and the patient has completed the study.

The database will contain indirectly nominative data on the sensitive subject of fecal incontinence and the therapy for a relatively small number of patients. Accordingly, this study falls within the scope of Article IX of the Law of January 6, 1978 modified by Law 94-548 of July 1, 1994 and Law 2004-801 of August 6, 2004, with respect to the processing of personal data for the purpose of research in the health sector.

Therefore, this database was subjected to an opinion request from the CCTIRS and an approval request from the CNIL.

This request specifies the nature of the data that will be collected, the treatment procedures, as well as the modalities of data retention, information and collection of the non-opposition of the patient to the conduct of this study.

A favorable opinion of the CCTIRS was obtained on March 17, 2011.
E.2.1.2 French National Medical Council (CNOM)

The physicians will be paid for participating in this study. However, pursuant to Article L.4113-6 of the Public Health Code, the following documents will be sent by the study Sponsor to the CNOM in order to obtain a favorable opinion:

1. Final version of the protocol of the observational study;
2. CRF;
3. The list of investigators.

The Sponsor of the observational study will send a registered letter to the CNOM declaring all financial relationships between the Sponsor and the physicians participating in the observational study.

Each physician acting as a member of the scientific committee has the responsibility to send a signed copy of the Financial Agreement to the French Departmental Medical Council (CDOM, Conseil Départemental de l’Ordre des Médecins) to which he/she is directly affiliated.

E.2.2 Patient Data Release Form and Non-opposition to the Conduct of the Study Form

The individuals participating in this study will be informed of the nature of the data transmitted, the objectives of the observational study, the anticipated use of the data, the persons who will receive the data, and their rights to access and rectify the data, as well as their right of opposition. This information will be provided to the patients in a printed document entitled “Patient Data Release Form” (see Appendix 1). They will be asked to read this document before data can be collected on them. The date of receipt of the non-opposition of the patient to the conduct of this study will be entered in the eCRF, and the original “Patient Data Release Form” signed by the patient will be filed at the study site.

E.2.3 Data Security

The questionnaire used for the electronic data collection will be developed in partnership with Medsharing, a company completely devoted to the development of internet tools for the conduct of clinical and observational studies. Medsharing is ISO9001 version 2008 certified for all its management and engineering procedures.

The Medsharing software is used to manage the design of the eCRF, assisted and automatically-controlled data entry, the follow-up of patients, real-time monitoring and data management, and to export selected data in standard formats (SAS, Excel, etc.) at any time.

Each person involved in the conduct of the study (investigators, clinical research associates, data managers and project managers) has access to distinct datasets using an individual password.
This eCRF does not require the installation of the software at the investigators’ or managers’ sites, does not require the installation of a server machine at the investigators’ or managers’ sites, and does not require the installation of the software on the computers used for data collection.

**E.3 Regulations and Good Practices in Epidemiology**

This study will be conducted in accordance with the applicable legislation and regulations which govern the conduct of medical research and the rights of the patient. In particular, the conduct of the study will follow the Guidelines for Professional Standards and Good Epidemiological Practice redacted in December 1998 by the Association des épidémiologistes de langue française (ADELF, Association of French-speaking Epidemiologists), the Association pour le développement des études et recherches épidémiologiques en santé travail (ADEREST, Association for the Development of Epidemiological Studies and Research on Workplace Health), the Association pour le dépistage des maladies dans la somme (ADEMA, Association for the Study of the Epidemiology of Animal Diseases) and the Association pour le développement de l’épidémiologie de terrain (EPITER, Association for the Development of Field Epidemiology), and updated in 2007, according to the principles of the Declaration of Helsinki (October 2008) for medical research and the applicable legislation and regulations in force in France. The principles of the Declaration of Helsinki are implemented during the procedure of non-opposition of the patient to the conduct of this study, the authorization procedure for the conduct of the study, the training procedure for the study personnel, patient enrollment into the study, and in the publication plan, etc.

All the devices used in the study have been approved by the regulatory authorities for their use in clinical practice, bear the CE marking, and are used in accordance with their indication for use. The devices are manufactured in accordance with the Directive sur les Dispositifs Médicales Actives Implantables (Directive for Active implantable medical devices) (90/385/EEC) and compliant with the applicable legislation and regulations in France.

**E.4 Study Training**

**E.4.1 Training of the Medtronic Personnel**

The Sponsor has the responsibility of providing appropriate training on the study to the Medtronic personnel designated to conduct the initiation visits, to train the site personnel, and to conduct the Monitoring and study closure visits.
E.4.2 Training of the Investigators

Before the initiation or participation of a site into the study, Medtronic will ensure that the personnel and investigators involved in the collection and entry of the study data receive proper training. The training will focus on the study procedures, data collection, recording and notification of the adverse events, the electronic data collection system, etc.

E.5 Management of Study Material

The study training material will be sent to the sites (Clinical Study Protocol and CRF). There will be no procedure implemented for the management of the Interstim® neuromodulator. This observational registry does not interfere with the current practice and the device is used in accordance with the indication approved by the HAS. The sites will receive the Interstim® material through the usual distribution process.

F METHOD

The HAS requested the creation of an exhaustive registry including all sites practicing this therapy and all the patients treated and followed for about a year after implantation. This registry may eventually be extended. Therefore, this is a prospective study comprised of an inclusion period of 46 months and a follow-up period of 9–15 months after the decision of the multidisciplinary committee regarding the permanent implant.

For each patient, data will be collected at the inclusion, the Baseline (or Initial) visit and the Test visit. For the patients who will receive a permanent implant, data will also be collected at the Implantation visit, and the Follow-up visit taking place 1–3 months after the implantation, 4–8 months after the implantation and 9–15 months after the implantation. For the patients who will not receive a permanent implant, data will be collected at the Follow-up visit taking place 4–8 months after the decision of the multidisciplinary committee regarding the permanent implant.
**F.1 Schedule of the Visits and Data Collected**

Table F.1 presents the schedule of the visits and the data collected, an ‘X’ indicating the evaluations that will take place at each visit.

<table>
<thead>
<tr>
<th>VISITS</th>
<th>Screening</th>
<th>MC</th>
<th>Baseline</th>
<th>Test</th>
<th>Permanent implant**</th>
<th>Follow-up visits</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-opposition of the patient to the conduct of the study</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Verification of the eligibility criteria</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reason for no enrollment*</td>
<td>X*</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Demographic data</td>
<td></td>
<td>x</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Characteristics of the disease</td>
<td></td>
<td></td>
<td>x</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Surgical and obstetric history</td>
<td></td>
<td></td>
<td></td>
<td>x</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Previous FI treatments</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clinical assessment (bowel diary and retention period)</td>
<td>x x</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patient satisfaction</td>
<td></td>
<td>x</td>
<td>x</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wexner incontinence score</td>
<td></td>
<td></td>
<td>x</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FIQL score</td>
<td></td>
<td>x</td>
<td></td>
<td>x</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Functional assessment</td>
<td>x x</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Specializations represented at the MC</td>
<td>x</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Type of lead implanted</td>
<td></td>
<td>x</td>
<td></td>
<td>x</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Specialization of the operator</td>
<td></td>
<td></td>
<td>x</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Position of the lead</td>
<td></td>
<td>x</td>
<td></td>
<td>x</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stimulation settings</td>
<td></td>
<td></td>
<td>x</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Implantation data</td>
<td></td>
<td></td>
<td>x</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patient status</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reimplantation</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adverse events</td>
<td></td>
<td>x</td>
<td></td>
<td>x</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Modification of the implanted system</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>**</td>
</tr>
</tbody>
</table>

**Table F.1:** Data to be collected at each visit. Please note that the windows of the follow-up visits will follow the clinical practice of the study site. MC: multidisciplinary consultation; FI: fecal incontinence; *: only for the patients indicated for the stimulation test, but not enrolled in the study; **: only for the patients included in the Primary Population.
**F.1.1 Inclusion Visit**

During a multidisciplinary consultation, all the patients indicated for the stimulation test and not opposed to the conduct of the study, and who meet all of the inclusion criteria and none of the exclusion criteria, will be included in the registry.

During the Screening Visit, a bowel diary will be given to the patients included in the registry. This diary will be completed for three weeks and then entered into the eCRF at the Baseline visit.

**F.1.2 Data Collected from the Non-enrolled Patients**

The tracking list of non-enrolled patients will only record the date and reason for not enrolling them in the study: omission of enrollment or lack of time, refusal, or impossibility to conduct a long-term follow-up of the patient.

**F.1.3 Initial (Baseline) Visit**

During the Initial (Baseline) visit, after confirmation of the non-opposition of the patient to the conduct of this study, the following data will be collected:

- Demographic data;
- Characteristics of the disease;
- Surgical and obstetric history;
- Previous treatments for fecal incontinence;
- Clinical assessment, including:
  - bowel diary over the last three weeks;
  - retention period;
  - Bristol scale;
- Wexner score;
- Score of the FIQL quality of life questionnaire;
- Functional Assessment, including:
  - Anorectal manometry;
  - Markers transit.
- Adverse events.
F.1.4 Test Visit

The test will be performed at the site per the site’s routine practices and following the indications specified in the User Manual. The following data will be collected during the Test visit:

- Characteristics of the test
- The specializations of the physicians participating in the test and analysis of the result.

A bowel diary will be given to the patients who will complete it during the three weeks after the Test visit, and these data will be entered at the end of the testing period.

The decision to proceed with the permanent implant will be based on the bowel diary and the overall impression of the patient regarding his/her possible improvement during the test.

The patients suitable for the permanent implant will be assigned to the ‘Primary Population’, whereas the patients not suitable will be assigned to the ‘Secondary Population’.

F.1.5 Implantation Visit

The permanent implant procedure will be performed on the Primary Population at the end of the testing period, per the site’s routine practices and the indications specified in the User Manual. Data will be collected on the implant procedure and stimulation settings.

F.1.6 Follow-up Visits at 1–3 Months, 4–8 Months and 9–15 Months

Follow-up data will be collected 1–3 months, 4–8 months and 9–15 months after the permanent implant procedure for the Primary Population, and only 4–8 months after the negative implantation decision for the Secondary Population.

Table F-1 indicates the data that will be collected at each follow-up visit.

The following data will be collected during the follow-up visits:

- Patient status;
- Adverse events;
- Clinical assessment, including:
  - bowel diary over the last three weeks;
  - retention period;
  - Bristol scale;
- Wexner score;
- FIQL score;
- Functional assessment, including:
  - Anorectal manometry;
  - Markers transit.
• Stimulation settings if the neurostimulator is reprogrammed;
• Date of the next follow-up visit (if applicable).

A bowel diary will be given to the patient before each visit. This diary will be completed during the last three weeks preceding the next follow-up visit, and then given back to the patient at each visit.

The quality of life questionnaire FIQL will be identical for each point.

The ‘Adverse Event’ form that will be completed in case of a complication (for more details, see section ‘F.5 Adverse Events’), whereas the ‘Reimplantation’ form will be completed as needed.

To minimize the number of patients lost to follow-up, patients will receive a phone call three weeks before the scheduled date of the visit to remind them the date of their next visit and to complete the bowel diary and the quality of life questionnaire.

Medtronic hired the CRO Chiltern to set up a call center for this purpose. To do this, the sites will need to provide to the CRO the names and telephone numbers of all the patients included in the study (Primary Population and Secondary Population).

F.2 Protocol Deviations

All the protocol deviations must be recorded in the specific form entitled ‘Protocol Deviations’.

A protocol deviation is defined as an event during the study that does not occur according to the protocol requirements. All protocol deviations must be documented as soon as the person involved in the study is notified.

Protocol deviations may be identified by several sources, for instance during the verification of the forms, phone conversations or Monitoring site visits.

Protocol deviations are frequently associated with the non-opposition of the patient to the conduct of this study, potential amendments to the study protocol requested by the HAS during the study, and tests or procedures indicated in the protocol that were not conducted.

Specific examples, including, but not limited to:

• failure to obtain the written non-opposition to the conduct of the study from the patient before his/her study participation;
• failure to obtain the appropriate regulatory approvals before the patients are included in the study;
• patients included in the study who do not meet the inclusion and exclusion criteria;
• patients included in the study who are not followed in accordance with the clinical practice of the site;
• patients not attending to a follow-up visit scheduled in accordance with the clinical practice of the site (missed visit);
• the source data are permanently lost.

F.3 Protocol Amendments

This protocol will not be modified without obtaining the approval of the regulatory authorities to implement the suggested amendments.
Moreover, once the study is launched, any modification of the protocol must be validated by the Scientific Committee of the Study.

F.4 Data Collection Procedure

The data will be collected by the clinicians using an electronic Case Report Form (eCRF). The clinicians must ensure that the eCRFs and other study reports are completed correctly and in time. All data the recorded in the eCRFs that were obtained from the source documents must be compatible with these forms. Otherwise, the discrepancies must be justified by a written justification, signed and dated by the clinician, and filed in the medical record of the patient.

The eCRFs and other study reports are completed by authorized personnel only. The eCRFs must be signed by the investigators, as indicated in the Delegated Task List (DTL) available in the Investigator Site File (ISF).

The electronic data collection (EDC) system maintains an audit trail of all the data entered, modified, or corrected in the forms. If a person authorized to complete the forms modifies data of a form already signed, this form must be signed again by the clinician to validate the changes.
### F.4.1 Data Submission

This table specifies when the clinicians could enter the data into the electronic forms:

<table>
<thead>
<tr>
<th>Data type</th>
<th>Submission deadline</th>
<th>eCRF to complete</th>
</tr>
</thead>
<tbody>
<tr>
<td>Notification of the new inclusion</td>
<td>Five business days starting on the signature date of the Patient Data Release Form and Non-Opposition to the Conduct of the Study Form</td>
<td>“Inclusion in the study”</td>
</tr>
<tr>
<td>Baseline data</td>
<td>15 business days starting on the date of the Baseline visit</td>
<td>“Baseline”</td>
</tr>
<tr>
<td>Test data</td>
<td>15 business days starting on the date of the Test visit</td>
<td>“Test”</td>
</tr>
<tr>
<td>Implantation data</td>
<td>15 business days starting on the date of the Implantation visit</td>
<td>“Implantation”</td>
</tr>
<tr>
<td>Patient’s personal data</td>
<td>5 business days starting on the date of the Implantation visit</td>
<td>“Patient’s personal data”</td>
</tr>
<tr>
<td>Date of the next Follow-up visit</td>
<td>3 business days starting on the date the Follow-up visit was conducted</td>
<td>“Schedule of the Follow-up visits”</td>
</tr>
<tr>
<td>Follow-up data</td>
<td>15 business days starting on the date the Follow-up visit was conducted</td>
<td>“Follow-up”</td>
</tr>
<tr>
<td>Modification of the date of the Follow-up visit</td>
<td>3 business days starting on the decision date of the modification</td>
<td>“Schedule of the Follow-up visits”</td>
</tr>
<tr>
<td>Adverse events data</td>
<td>see section F.5.2.2</td>
<td>“adverse events”</td>
</tr>
<tr>
<td>Modification data of the implanted system</td>
<td>15 business days starting on the modification date</td>
<td>“Modification of the implanted system”</td>
</tr>
<tr>
<td>Protocol deviation</td>
<td>3 business days if the deviation occurred to protect the patient’s</td>
<td>“Protocol deviation”</td>
</tr>
</tbody>
</table>
Table F.2: Deadline proposed to submit the data and to complete the related CRFs.

<table>
<thead>
<tr>
<th>Event</th>
<th>Deadline</th>
<th>Note</th>
</tr>
</thead>
<tbody>
<tr>
<td>Failure to obtain the non-opposition of the patient to the conduct of the study</td>
<td>3 business days starting on the date of discovery</td>
<td>“Protocol deviation”</td>
</tr>
<tr>
<td>Withdrawal of patient from study</td>
<td>5 business days starting on the date of awareness of death/withdrawal</td>
<td>“Study withdrawal”</td>
</tr>
<tr>
<td>Death of the patient</td>
<td>see section F.5.2.3</td>
<td>“Death of the patient”</td>
</tr>
</tbody>
</table>

NB: The data collection system will grant different access to each system user: the Sponsor will have access to the anonymized data of the patients, but not to the data entered in the “Patient's personal data” form. Moreover, Chiltern, which is responsible for the call center, will have access to the patient's personal data (in the CRF “Patient's personal data”) and the schedule of follow-up visits, but not to the clinical data of the patients. The clinicians will have access to all the information related to the patients of their site and will be authorized to modify them.

F.5 Adverse Events

F.5.1 Definition and Classification of Adverse Events

The following adverse events will be collected for the study, as they represent one of the secondary objectives (for more details, see section C.2.2.5 Complications and Adverse Events):

- Adverse events;
- Serious adverse events;
- Adverse device effects;
- Serious adverse device effects.

However, the clinicians will classify the adverse events using the definition presented by EN ISO14155 (2011).

The following definitions will be used by the Sponsor to classify each adverse event:

**Adverse event – AE (ISO14155:2011 3.2):**
Any adverse clinical manifestation, unintentional disease or injury, or untoward clinical sign (including abnormal laboratory findings) in subjects, users or other persons, whether or not related to the investigational medical device.

NOTE 1 This definition includes the events related to the investigational medical device or the comparator.

NOTE 2 This definition includes the events related to the procedures involved.

NOTE 3 For the users or other persons, this definition is restricted to events related to the investigational medical device.

**Adverse device effect - ADE (ISO14155:2011 3.1):**

Adverse event related to the use of the medical device investigated.

NOTE 1 This definition includes adverse events resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation, or any malfunction of the investigational medical device.

NOTE 2 This definition includes any event resulting from use error or intentional misuse of the investigational medical device.

**Serious Adverse Event – SAE (ISO14155:2011 3.37):**

Adverse event that

a) led to death,

b) led to serious deterioration in the health of the subject, that either resulted in,

1) a life-threatening illness or injury, or

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

3) in-patient or prolonged hospitalization, or

4) medical or surgical intervention, to prevent life-threatening illness or injury or permanent impairment to a body structure or body function;

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

NOTE Planned hospitalization for a pre-existing condition, or a procedure required by the CIP, without serious deterioration in health, is not considered a serious adverse event.

**Serious adverse device effect – SADE (ISO14155 :2011 3.36):**

Adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event.

**Incidents**

Aside from adverse events, all events that may be considered an incident must be reported in accordance with the procedures stipulated in MEDDEV 2.12-1 Rev. 6.

Each event meeting the three criteria listed below are considered INCIDENTS and must be reported to the regulatory authorities:
1. the event occurred:
This also includes the situations where the test procedures performed on the devices, the evaluation of the data transmitted by the device, or each clinical information identifies a factor that may lead, or led, to an event. Specific examples, including, but not limited to:

- Defect in the system or the characteristics or performance of the device. A defect must be considered a failure of the device to operate as expected or a misuse with respect to the User Manual.
- Tests performed on the device leading to a percentage of false positive or false negative results inconsistent with the declared performances;
- Unexpected and adverse reaction or unexpected side-effect;
- Interactions with other substances or products;
- Degradation/destruction of the device;
- Inappropriate therapy;
- Errors on the label, in the instructions for use and/or in the promotional material.
  Errors include omissions and deficiencies. Omissions include a lack of information on matters that should generally be known by users.

2. the device is suspected of having contributed to the incident

3. the event led, or might have led, to one of the following consequences:

- Death of the patient, the user or other persons;
- Serious deterioration in health of the patient, the user or other persons;
  Serious deterioration in health may include:
    a. a life-threatening illness or injury, or
    b. a permanent impairment of a body structure or body functions, or
    c. in-patient or prolonged hospitalization, or
    d. medical or surgical intervention, to prevent life-threatening illness or injury or permanent impairment to a body structure or body function,
    e. fetal distress, fetal death or a congenital abnormality or birth defect.

F.5.2 Recording and Publication of Adverse Events

Data related to adverse events will be collected during the study (from the signature date of the Patient Data Release Form until the date of patient study exit), and will be notified to Medtronic using the electronic form entitled “Adverse Event” in the electronic data collection system. All adverse events must be notified by entering the data into the electronic form entitled “Adverse Event”.

The data entered in the eCRF will include a description of the event, the start date of the event, the link between the event and the procedure, the link between the event and the device, the actions taken after the event, the outcome of the event, and the date the investigator was notified about the event.

For all the adverse events, all the available information must be recorded in the “Adverse event” form.

If the investigator urgently needs additional information from the Sponsor, the investigator may contact the Project Manager or the Study Manager of Medtronic (contact information available in section I.1 Study Members).

All adverse events must be reported immediately.

**F.5.2.1 Adverse Events Review Process**

All adverse events must be examined by the Study Manager of Medtronic. This review will determine if the adverse event has to be reported in compliance with the regulatory requirements (see Table F.3). The Sponsor will ensure the immediate transmission of the “Adverse event” forms in order to comply with the general regulatory requirements.

If the adverse event is related to the study device bearing a CE marking, the Study Manager of Medtronic will inform Medtronic Product Performance International West (headquartered at Heerlen, THE NETHERLANDS) of the adverse device effect for a quick examination, as well as the competent authorities if necessary.

<table>
<thead>
<tr>
<th>Investigator</th>
<th>Medtronic</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Adverse event (AE)</strong></td>
<td>Report all AEs by completing the <em>Adverse Event</em> electronic form</td>
</tr>
<tr>
<td><strong>Serious adverse event (SAE)</strong></td>
<td>Report all SAEs by completing the <em>Adverse Event</em> electronic form</td>
</tr>
<tr>
<td><strong>Adverse device effect (ADE)</strong></td>
<td>Report all ADEs by completing the <em>Adverse Event</em> electronic form</td>
</tr>
<tr>
<td><strong>Serious adverse device effect (SADE)</strong></td>
<td>Send immediately all available information as soon as you are aware of the event by completing the electronic form <em>Adverse Event</em></td>
</tr>
</tbody>
</table>

**Table F.3:** Communication procedures for adverse events.
F.5.2.2 Follow-up on the Adverse Events

All adverse events occurring during the study must be monitored in accordance with the guidelines of the Good Medical Practice until they are resolved, or deemed clinically not significant, or if it is a chronic condition, until it has been completely characterized.

All the follow-up data must be entered in the eCRF. Any change in severity, the suspected relation to the device, the required surgeries, and the final outcome must be evaluated at each visit (or more frequently, if needed).

F.5.2.3 Death of the Patient

If a patient dies during the study, the event will have to be reported as a serious adverse event (SAE) using the communication procedures described for SAEs. The death of the patient must be documented in the form “Study Exit”. The date and primary cause of death, including the results of the post-mortem examination, if applicable, will be included. This form will indicate the time of death and document the causal link between the death and the implant or the follow-up procedures.

F.6 Device Removal and Return Procedure

A device previously implanted cannot be reused. The explanted products must be returned to Medtronic in appropriate and approved packaging. Careful analysis of the returned products may provide insightful information on the performance of the device. Return packaging will be provided to the sites upon request.

F.7 Follow-up of the Patients

If a patient withdraws from the study, the reason for withdrawal will be recorded in the eCRFs and the medical record of the patient. If the patient’s withdrawal is due to a safety issue or a lack of efficacy, the patient will be asked to continue to come to the follow-up visits for the collection of safety-related data.

The patients will not be excluded from the analyses. For all the patients who prematurely exit the study, the extrapolation technique for missing data LOCF (Last Observation Carried Forward) will be used, namely for the primary analyses.
G LOGISTICAL ASPECTS

G.1 Preparation of the Registry

This phase involves:
- Set up of the protocol and CRFs used for the Inclusion visit, the Follow-up visits and reporting of adverse events;
- Management of the regulatory aspects (CCTIRS and CNIL).

Design and maintenance of the eCRF, as well as data hosting, carried out by Medsharing, a company specialized in the development of online integrated management systems (IMS) for clinical studies.

This phase involves:
- The development of electronic data collection tools and the implementation of the follow-up procedures of the study;
- Communication with the sites in order to present the study and its procedures and to schedule the Initiation visit;
- The transmission of an access code and password by the company managing the eCRF, in order to test them during the Initiation visit;

G.2 Data Quality Control

This multi-center study will be subjected to quality control by the Sponsor. This control will be performed at various levels.

G.2.1 Initiation of the Study Sites

The study sites will be initiated by the Monitors or the Study Manager, who will have the responsibility of verifying that the site meets the requirements to participate in this study.

G.2.2 Exhaustivity

Exhaustivity will be verified with respect to the patients’ inclusions in the study and the follow-up data.

G.2.2.1 Inclusions:

The number of patients included in the study will be cross-referenced with the sales data of Medtronic. The sites will be contacted by the Sponsor if missing inclusions are
detected, compared to the activity level of a site known by Medtronic. During these contacts, if some patients are not included in the study, the reasons will be documented.

G.2.2.2. Follow-ups:

Follow-up reports will be sent by the Study Manager to the study sites every two months, including a list of the patients included, the follow-up visits completed and those that will be conducted in the next two months. If follow-up forms are not entered within two months, the Project Manager will send a reminder to the study sites by regular mail or email. To minimize the number of patients lost to follow-up, patients will receive a follow-up phone call to remind them of the date of their next visit, and to complete the bowel diary and the quality of life questionnaire (FIQL). The phone calls will be made three weeks before the follow-up visit: for each visit, the call center will attempt to contact the patient three times. The call center will communicate only with the patient, and no voice message will be left on the answering machine.

To do this, the study sites will need to give to the call center the names and telephone numbers of the implanted patients. The names and telephone numbers will be entered in a secure database and will be used only to call the patients.

G.2.3 Data Quality

The data entered by the clinicians in the electronic database will be subjected to quality control. This control will be performed using the procedures described in the Monitoring Plan. If key data are missing or inconsistent, edit-checks will be redacted and sent by the electronic data collection system.

G.2.4 Keep the Study Sites Informed

The sites will be informed on a regular basis on the progress and results of the study through newsletters sent by regular mail or email every three months.

G.3 Monitoring

The Sponsor is responsible for ensuring that the monitoring procedures are conducted in an appropriate manner. The trained personnel designated by the Sponsor will conduct monitoring visits to ensure that the study is conducted according to the Clinical Investigation Plan, the Clinical Trial Agreement signed between the site/clinician and the Sponsor, and the good practices in epidemiology.
G.3.1 Specific Responsibilities of the Supervisor

This multi-center study will be subjected to quality control by the Sponsor. The role of the monitor will be to participate in the initiation of the implanting study sites and to ensure quality control, according to the procedures outlined in section G.2 Data Quality Control.

G.3.2 Monitoring Procedures

G.3.2.1 Site Initiation Visits

A Site Initiation visit will be conducted by the Study Manager or a monitor or a designated person at each site. The objectives of these visits are as follows:

- Explain the conduct of the study: the procedures for patient inclusion, patient information and follow-up;
- Provide technical training to the users of the electronic data collection system;
- Test in real-time the use of the CRFs.

During this Site Initiation visit, the following information will be collected: starting date of the Interstim® therapy practice, the specialization of the clinicians involved, and the organization of the multidisciplinary consultation.

These visits will be conducted periodically to recruit new sites starting to practice this therapy during the inclusion period.

G.3.2.3 Monitoring Visits during the Study

The monitoring visits conducted during the study will cover the procedures described in the Monitoring Plan. Their objective is to verify the adherence of the sites to the Study Design, the source data documents (accuracy, completeness, readability and omissions), and the written non-opposition documents of the patients.

G.3.2.4 Close out Visits

The Study Manager, the monitors or designated persons may close the study in person or by telephone.

G.3.3 Audits and Inspections

Aside from the regular monitoring visits, the Sponsor may conduct audits at the study sites. The objective of these audits is to verify the performance of the study sites regarding all activities of
the study. The frequency of the audits will not be dependent on the Medtronic personnel directly involved in the study.

In addition, the regulatory authorities may also conduct inspection visits at the study sites. The investigator and/or study site must allow Medtronic and the regulatory authorities to access the source data and other documents (in compliance with the applicable regulations) in order to conduct monitoring visits, audits and regulatory inspections. The Sponsor may choose to conduct audits at random during the study to ensure the quality of all aspects of the study.

Furthermore, the study sites could be inspected by the regulatory authorities: each visit notification by the regulatory institutions must be sent as soon as possible to the Study Manager and the study site specialists. The study sites will have to allow the abovementioned authorities to examine the source data and other documents. Also, the Principal Investigators will be asked to be available during these inspections.

G.4 End of Study

G.4.1 Scheduled Study Closure

Study closure is initiated by a close out letter. The study will be closed:

- when the conditions defined in the Clinical Investigation Plan are fulfilled, or
- by decision of the Sponsor and/or the regulatory authorities.

Study termination will be definitive after the distribution of the Final Report or after the last payment.

G.4.2 Premature Closure or Suspension of the Study

The Sponsor may decide to prematurely terminate or suspend the study. If the study is prematurely terminated or suspended, the Sponsor will promptly inform the investigators of the termination or suspension and will specify the reasons that motivated this decision. All the regulatory authorities involved will also be notified.

The possible causes that may lead to the premature termination or suspension of the study are:

- the risks for the included patients are higher than initially anticipated;
- by decision of the Sponsor or regulatory authorities.
G.4.3 Premature Closure or Suspension of a Study Site

The Sponsor may decide to terminate or suspend a study site. If a study site is prematurely terminated or suspended, the Sponsor will promptly inform the investigators of the closure or suspension and will specify the reasons that led to this decision.

The possible causes that may lead to the premature closure or suspension of a study site are:

- failure to activate the study site;
- recurrent non-compliance with the study procedures described in the Clinical Investigation Plan (for example, non-compliance with the inclusion/exclusion criteria, non-compliance with the scheduled follow-up visits of the patients, etc.);
- low number of study inclusions;
- non-compliance with the terms of the Clinical Trial Agreement (for example, regarding data submission or completing the CRFs or addressing queries generated by the system);
- discovery of fraud or professional misconduct (according to the French Law);
- at the request of the investigator (for example, if the study site no longer meets the requirements to conduct the study).
H STATISTICAL ANALYSIS AND STUDY REPORTS

All derogations from this section and/or the Statistical Analysis Plan will be described and justified in the Final Report.

H.1 Statistical Analyses

The study will be designed to minimize the effects of the protocol deviations and missing data, and all the patients for whom the data can be evaluated will be included in the analyses. The statistical analyses will be performed using the SAS statistical software version 9.1 and other statistical or graphics software.

For each qualitative variable addressed at each step, the analysis will present the number of missing data, the sample size and the percentage for each modality, as well as the 95% confidence intervals.

For each quantitative variable addressed at each step, the analysis will present the number of missing data, the sample size, the mean and standard deviation, the median, the minimum, the maximum and the quartiles.

A patient will be considered included in the registry if all the inclusion criteria, and none of the exclusion criteria, are met and the stimulation test is conducted in prevision of an implantation.

The statistical analyses will be performed on the Primary Population (the patients with a positive stimulation test and implanted with the neurostimulator) and the Secondary Population (the patients with a negative stimulation test).

At each step of the analysis, the data analyzed will account for the situation of the patient, based on the latest information and the follow-up duration for the patients lost to follow-up.

The missing data of each patient will be presented in a separate table. Extrapolation techniques for missing data, such as LOCF (Last Observation Carried Forward), will be used only for the primary analysis and some of the secondary outcome measures, depending on the results obtained from the primary analyses.

Final analysis:
The final analysis will be performed when the last implanted patient of the registry has completed the 9–15 months follow-up visit.

The outcome measures will be analyzed as defined in section ‘C.2 Outcome Measures’.
Interim Analysis:
This is a non-randomized observational study. An interim analysis will be conducted at the end of the inclusion period, and after the 1–3 month follow-up visit, to provide a description of the patients included in the study. Details on the analyses are available in the Statistical Analysis Plan. The results of these Interim analyses will be presented and/or published.

H.1.1 Inclusion Data

The analysis of the inclusion data will include a description of the study sites, namely the start date of implantations for fecal incontinence at that site, the number of patients included per site and the organization of each site, collected at the time of the study initiation.

The entire cohort of enrolled patients will be described with respect to all the characteristics investigated.

This description will notably allow the definition of the treatment indications and compliance with the predicted indications.

The simple descriptive analysis will be performed to describe:

- the characteristics of the patients and their disease at the time of implantation (cause and type of incontinence, previous treatments), in order to allow comparison of the characteristics of the implanted patients with the indications retained in the opinion of the CNEDIMTS
- the pre-implantation assessment and its results
- the test results
- the early complications (during the implant procedure and the first month of follow-up)

A particular attention will be paid to complications associated with death or requiring hospitalization. All complications and their consequences (hospitalization, reversible nature and possible relation to with the device) will be described.

H.1.2 Follow-up Data

The analysis of the follow-up data will provide a description of the short- and long-term outcomes, according to the primary and secondary outcome measures. These analyses will take into account the follow-up duration and the patients lost to follow-up.

The analysis of the follow-up data collected at the 3–6 months and 9–15 months visits will document the short- and long-term benefits.

In addition, the complications will be quantified and described using the same approach as for the implantations.
Survival analyses will be conducted on the follow-up data at each step of the analyses in order to document survival and device maintenance, taking follow-up duration into account. If data are missing for the 3–6 months follow-up visit, and for the 9–15 months follow-up visit for some patients, mixed model analyses will be used to consider all the patients and all the data collected.

**H.2 Publications**

**H.2.1 Reports**

Two reports will be prepared:

- the first report on the inclusion data and the 1–3 months follow-up data (interim report);
- the second report after 9–15 months of follow-up, including the 4–8 months and 9–15 months follow-up data. This will correspond to the Final Study Visit, unless the inclusion period and/or follow-up period is/are extended.

The reports will describe again the method and the conduct of the study, and will present all the data available. The reports will also include a description of the study sites offering these treatments.

**H.2.2 Publications and Presentation of the Results**

There will be no Publication Committee. The publications and presentations of the study results will be supervised by Medtronic to ensure that all available data are included. We expect to present and/or publish:

- the results generated from the interim analysis;
- the results generated from the final analysis;

The authors of each publication will be assigned depending on their significant contribution to the data acquisition, analysis and interpretation, or the drafting of the articles/presentations or their critical review, according to the Publication Plan that will be prepared during the study.

The Publication Plan will be developed in accordance with the Vancouver principles (The Uniform Requirements for Manuscripts Submitted to Biomedical Journals: Writing and Editing for Biomedical Publication, ICMJE, October 2008), defined by editors of major scientific journals. Each publication or presentation of the results (interim or final), summary, or other material will have to be reviewed by the Sponsor before their submission.
I STUDY MANAGEMENT

I.1 Medtronic Personnel Involved in the Study

The following table identifies the team members of the clinical study, including their position, contact information and organization. The composition of the team can be modified during the study. For this reason, regular updates will be sent to the study sites.

<table>
<thead>
<tr>
<th>Position</th>
<th>Manager/Organization</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study Sponsor</td>
<td>Medtronic International Trading Sàrl</td>
</tr>
<tr>
<td></td>
<td>Route du Molliau 31</td>
</tr>
<tr>
<td></td>
<td>CH-1131 Tolochenaz, Switzerland</td>
</tr>
<tr>
<td>Project Manager</td>
<td>Charlotte Pollet</td>
</tr>
<tr>
<td></td>
<td>Medtronic International Trading Sàrl</td>
</tr>
<tr>
<td></td>
<td>Route du Molliau 31</td>
</tr>
<tr>
<td></td>
<td>T.: + 41 79 7088145</td>
</tr>
<tr>
<td></td>
<td>✉: <a href="mailto:charlotte.pollet@medtronic.com">charlotte.pollet@medtronic.com</a></td>
</tr>
<tr>
<td>Study Manager</td>
<td>Claudia Campo</td>
</tr>
<tr>
<td></td>
<td>EMEA Regional Clinical Center</td>
</tr>
<tr>
<td></td>
<td>Medtronic Clinical Research Institute</td>
</tr>
<tr>
<td></td>
<td>Piazza I. Montanelli 3</td>
</tr>
<tr>
<td></td>
<td>T.: +39 347 3265139</td>
</tr>
<tr>
<td></td>
<td>✉: <a href="mailto:claudia.campo@medtronic.com">claudia.campo@medtronic.com</a></td>
</tr>
<tr>
<td>Data management</td>
<td>Virginie Gely</td>
</tr>
<tr>
<td></td>
<td>EMEA International Clinical Operations</td>
</tr>
<tr>
<td></td>
<td>Medtronic International Trading Sàrl</td>
</tr>
<tr>
<td></td>
<td>Route du Molliau 31</td>
</tr>
<tr>
<td></td>
<td>T.: +41 21 803 8069</td>
</tr>
<tr>
<td></td>
<td>✉: <a href="mailto:virginie.gely@medtronic.com">virginie.gely@medtronic.com</a></td>
</tr>
<tr>
<td>Installation and Maintenance of the Data</td>
<td>MedSharing</td>
</tr>
<tr>
<td>Collection System</td>
<td></td>
</tr>
<tr>
<td>Statistics</td>
<td>Abdallah Abouihia</td>
</tr>
<tr>
<td></td>
<td>Medtronic International Trading Sàrl</td>
</tr>
<tr>
<td></td>
<td>Route du Molliau 31</td>
</tr>
<tr>
<td></td>
<td>T.: + 41 79 557 9163</td>
</tr>
<tr>
<td></td>
<td>✉: <a href="mailto:abdallah.abouihia@medtronic.com">abdallah.abouihia@medtronic.com</a></td>
</tr>
<tr>
<td>Reimbursement</td>
<td>Béatrice Petzold</td>
</tr>
<tr>
<td></td>
<td>Medtronic France SAS</td>
</tr>
<tr>
<td></td>
<td>27 Quai Alphonse Le Gallo</td>
</tr>
<tr>
<td></td>
<td>T.: +33 1 55381703</td>
</tr>
<tr>
<td></td>
<td>✉: <a href="mailto:beatrice.petzold@medtronic.com">beatrice.petzold@medtronic.com</a></td>
</tr>
<tr>
<td>Monitoring</td>
<td>MCO CRAs</td>
</tr>
<tr>
<td></td>
<td>EMEA International Clinical Operations</td>
</tr>
<tr>
<td></td>
<td>Medtronic Clinical Research Institute</td>
</tr>
<tr>
<td></td>
<td>Endepolsdomein 5</td>
</tr>
</tbody>
</table>
Moreover, Medtronic qualified personnel not directly involved in the conduct of the study may provide technical support during the test, the implant procedure or the device follow-up sections.

As anticipated in sections E.2 Regulatory Approvals, F.1.6 Follow-up Visits at 1–3 Months, 4–8 Months and 9–15 Months and G.2.2.2 Follow-ups, the Sponsor uses the call center services provided by the company Chiltern.

In addition, other study offices (Contract Research Organization, CROs) may be mandated to conduct other study-related activities if internal resources are unavailable. Information on the mandated CROs will be provided separately.

### I.2 Advisory Committees

#### I.2.1 Scientific Committee

At the request of the HAS, a Scientific Committee was set up by the Sponsor.

The members of the Scientific Committee were selected by addressing the characteristics defined by the HAS [1]:

a. multidisciplinary and qualified, including experts in the investigated pathology and at least one epidemiologist or one pharmaco-epidemiologist or one methodologist or one biostatistician.

b. independent: none of the members can be an employee of the company sponsoring this study or the CRO conducting this study, or be a member of different HAS committees.

Therefore, this independent and multidisciplinary committee comprises a methodologist and several physicians with a large experience in the treatment of fecal incontinence. These physicians are gastro-enterologists, digestive surgeons and neurophysiologists.

The committee members are:

- Pr Laurent SIPROUDHIS, Gastroenterologist, Pontchaillou University Hospital, Rennes;
- Dr Henri DAMON, Gastroenterologist, Edouard Herriot Hospital, Lyon;
- Pr Jean-Luc FAUCHERON, Digestive surgeon, Grenoble University Hospital;
- Pr Anne-Marie LEROI, Neurophysiologist, Charles Nicolle University Hospital, Rouen;
- Pr Yann PARC, Digestive surgeon, Saint Antoine Hospital, Paris;
- Dr Anne-Laure TARRERIAS, Gastroenterologist, Medical Center, Paris 16ème;
- Dr François PIGOT, Gastroenterologist, Bagatelle Hospital, Bordeaux;
- Dr Gérard TAP, Physician and Methodologist, Toulouse.

The main duties of the Scientific Committee are:
to write and/or validate the study methodology: protocol, data collection sheets, statistical analysis plan

to validate all modifications brought to the protocol after the start of the study;

to follow the conduct of the study and support the participation of the study sites;

to write and/or validate the reports on the study results.

For example, if inclusion issues occur during the study, the Scientific Committee suggests solutions to address these difficulties (recruitment of additional sites or investigators, extension of the inclusion period, increase the number of patients included by each investigator, etc.) and validates the modifications brought to the protocol.

This Scientific Committee will not validate the events that occurred during the study and will not evaluate the imputability of the Interstim® system.

The Scientific Committee met before the start of the study to validate the scientific aspect and methodology of the protocol. Additional meetings are planned for the Scientific Committee to review the results of the interim analysis (that will be performed at the end of the inclusion period) and the final analysis, and as needed.


I.2.2 Other Advisory Committees

We do not anticipate the involvement of other advisory committees.
I.3 Reports and Documents Management

I.3.1 Study Documents Retention at the Sites

The investigator is responsible for the preparation (revision and signature) and the retention of the documents listed below.

All the documents below, except for the medical records of the patients, must be maintained in the Investigator Site File (ISF), meaning the study folder provided by Medtronic to the investigators or the appropriate patient’s folder. The ISF or patient’s folder must contain a note indicating the retention of the missing documents. Moreover, the following documents may be subjected to inspections and must be retained for a period of 2 years (or longer, depending on the recommendations of the Site Administration) after study closure (study closure will take place as described in section G.4 Study Closure):

- All study-related essential correspondence between the investigator and Medtronic;
- Files containing the patients history, including: the Patient Data Release Form signed and dated by the patient, the observations on the adverse events/adverse device effects, the medical history, the baseline data (in CFRs signed and dated), the documentation on the dates and reasons for the protocol deviations;
- Clinical Investigation Plan;
- Clinical Trial Agreement signed and dated;
- Curriculum Vitae of the investigators (signed and dated);
- Study training certificates for the study team members involved.

I.3.2 Responsibilities of the Investigators

The investigator is responsible for the preparation (revision and signature) and the submission of the CRFs, adverse events reports and protocol deviation reports to the Sponsor. Moreover, these informations are subjected to inspections and must be archived according to the abovementioned procedures: the clinicians must provide, at the possible request of the regulatory authorities, accurate and complete information on each aspect of the study.

Regarding data submission and the submission procedures, please refer to section F.4.2 Data Submission.
I.3.3 Documents Archived by the Sponsor

The following documents will be archived by the Sponsor in 15 years:

- The Clinical Project File including the SOP Audit Trail, the Clinical Management Plan and the Monitoring Plan
- All study-related essential correspondence with the investigators;
- The signed Clinical Trial Agreements;
- The Curriculum Vitae of the investigators, signed and dated;
- All anonymized CRFs submitted by the investigators, a copy of the Patient Data Release Form and Non-Opposition to the Conduct of the Study Form, and any other information provided to the patients enrolled in the study;
- Names of the study sites;
- Any correspondence with the regulatory authorities and the approval documents;
- Reporting forms for the adverse events and adverse device effects;
- Statistical analyses, results and anonymized databases;
- Final Study Report;
- Clinical Investigation Plan and study reports;
- Training documents of the site personnel and Medtronic personnel involved in the study.
I.3.4 Responsibilities of the Sponsor

Medtronic must prepare and submit all the documents listed in Table I-1 meticulously and promptly.

<table>
<thead>
<tr>
<th>Report</th>
<th>Submit to</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adverse Events (AEs), serious adverse events (SAEs) and adverse device effects (ADEs).</td>
<td>Medtronic will ensure that all AEs, SAEs and ADEs are reported according to the procedures outlined in section F.55 and reviewed with the investigators.</td>
<td></td>
</tr>
<tr>
<td>Serious adverse device effects (SADEs)</td>
<td>Regulatory authorities and, according to the risk perceived, to all the investigators</td>
<td>Medtronic will report all SADEs by following the standard vigilance procedure.</td>
</tr>
<tr>
<td>Premature closure or suspension of the study</td>
<td>Medtronic will announce the premature termination or suspension of the study in a prompt manner.</td>
<td></td>
</tr>
<tr>
<td>Deviations from the clinical study</td>
<td>Medtronic will ensure that all the deviations from the Clinical Investigation Plan identified will be examined and approved, will be reported in the CRFs and the Final Study Report, and that preventive and corrective measures will be taken.</td>
<td></td>
</tr>
<tr>
<td>Interim Study Report</td>
<td>The Interim Report will be submitted after the end of the inclusion period. The investigators will have the possibility to read and make comments, and they must sign the report. If an investigator disagrees with this report, his/her comments will be sent to the other investigators. The Principal Investigator of each site must sign the report. The report will be submitted to the regulatory authorities.</td>
<td></td>
</tr>
<tr>
<td>Final Study Report</td>
<td>The Final Report will be submitted within one year after the end of the study; likewise if the study is terminated prematurely. The investigators will have the possibility to read and make comments, and they must sign the report. If an investigator disagrees with the Final Report, his/her comments will be sent to the other investigators. The Principal Investigator of each site must sign the report. The report will be submitted to the regulatory authorities.</td>
<td></td>
</tr>
</tbody>
</table>

Table I.1: Responsibility of Medtronic for the Data.
I.3.4.1 Anticipated Schedule

The total duration of the study is determined by the inclusion period of 286 patients: we can reasonably expect an inclusion period of 46 months. In this case, the total duration of the study will be 60 months (46 months for the inclusion period and 9–15 months for the follow-up period of each patient).

The analysis of the inclusion data will be performed after the end of the inclusion period, and a first draft of the Interim Report containing all the data of the first three months of follow-up will be generated rapidly after 1–3 months of follow-up, in order for it to be available for the renewal folder of the reimbursement. The Final Report on the follow-up data collected at the 4–8 months and 9–15 months visits will be generated at the end of the study.

I.4 Miscellaneous

I.4.1 Insurance

Insurance is not necessary for this study.

I.4.2 Data Confidentiality

Pursuant to Article R 5120 of the Public Health Code, the physicians and all the persons that will collaborate in this study are bound by the obligation of professional secrecy with respect to the studies, the participants and the results obtained.

The names and telephone numbers of the patients lost to follow-up, which will be known by Chiltern to conduct reminders, will be destroyed at the end of the study.

J RISKS AND BENEFITS

J.1 Risks

All the devices used in this study were commercialized before the start of the study. Medtronic is not aware of significant problems with the products used. During this study, all the devices will be used according to the instructions described in the User Manual. As such, no additional risk is anticipated, aside from the usual risks associated with the routine implantation of the Interstim® system and the follow-up visits.
Furthermore, the patients will be treated according to the local practices of the study site, such that no additional test or follow-up visit will be requested. Consequently, no additional risk is associated with the participation to this study.

J.2 Possible Benefits

Aside from the usual clinical benefits of the sacral neuromodulation therapy with the Interstim® system, no other benefit is expected from the participation of the patients to this study.

K REFERENCES

12. Wexner S. et al. Sacral nerve stimulation for fecal incontinence. Results of a 120-patient


Appendix 1 - Patient Data Release Form and Non-Opposition to the Conduct of the Study Form

Patient Data Release Form
for the Post-Approval Follow-up Study on Sacral Neuromodulation
for the Treatment of Fecal Incontinence

Madam, Sir,

You will benefit from the implantation of a lead for the treatment of your incontinence problem. Since this therapy was recently implemented in France, the Haute Autorité de Santé (HAS, French National Authority for Health) has asked the manufacturer, MEDTRONIC, to conduct a study to evaluate the efficacy and tolerance of the treatment in routine practice. The physician that monitors your progress during this treatment participates in this study. Today, he/she would like to invite you to participate in a follow-up study aiming to evaluate at medium term, about one year, the efficacy of the Interstim® system for sacral neuromodulation.

Study Presentation
The objective of the study is to follow the patients after the implantation of this medical device. It should determine whether this therapy is properly used.

This study is proposed to all the patients benefiting from a lead implant for the treatment of their fecal incontinence, in all French centers qualified to practice this treatment.

This study is “non-interventional”, which means that you will be under no obligation (no additional consultation, treatment or examination) and you will not receive any direct or immediate benefits. It does not affect in any way the quality and choice of the treatment that you will receive or have received. Your participation in the study will not exceed 16 months, unless the HAS requests an extension of the registry. In that case, you will be informed by your physician.

This study will be conducted at about 35 French centers currently implanting this device. The data will be collected on about 300 patients.
The study Sponsor is the company Medtronic International Trading Sàrl - Route du Molliau 3 - CH-1131 Tolochenaz, Switzerland.

If you agree to participate, your physician will complete a questionnaire at each of your scheduled visits, meaning at the Initial visit and the Test visit. After these two visits, a committee of physicians will decide, based on your clinical data and your response during the test, if you are a suitable candidate for the permanent neurostimulator implant. If their decision is positive, you will receive a neuromodulator implant. Your physician will complete a questionnaire on the implant procedure, as well as follow-up questionnaires at 1–3 months, 4–8 months, and 9–15 months follow-up visits.

If their decision regarding the implant is negative, your data will only be collected by the physician during a visit which will take place 4–8 months after the decision not to give you an implant.

In all cases, the data collected will be related to your demographic data, your medical history, the safety and efficacy of the treatment and possible adverse events.

In all cases, Medtronic qualified personnel may provide technical support during the test, the permanent implant procedure and the follow-up visits.

If you agree by signing this document, your name and telephone numbers will be given to an organization outside of the hospital (named Chiltern, headquarters at 37 bis rue de Villiers - 92200 Neuilly sur Seine - France) that will have the responsibility of calling you three weeks before each visit. The purpose of these phone calls will be to remind you of the date of the visit and to bring the diary and the quality of life questionnaire that will be given to you by the physician with you to the visit.

Your acceptance, or your refusal, to participate in this study will be inconsequential for you and will not affect your medical care. Your participation in this study is voluntary and you can withdraw from the study at any time.

The physician that will follow you during the study may also decide to remove you from the study at any time, and without your prior consent, for example, if you miss several consecutive visits. In this case, the physician will inform you of his/her decision and explain the reasons.

Confidentiality and anonymity
a. For the clinical data collected during the study:

The clinical information related to your health status will be collected in a strictly confidential manner, and your anonymity will always be protected during computer data processing using an identification code. Your name will never appear on the data collection form. These data will be used
and processed manually and computationally by Medtronic (meaning the consortium of Medtronic Inc.).

Other stakeholders commissioned by Medtronic for the purpose of this study, such as data processing firms, the establishment where you are treated, your physician(s), health authorities or government agencies, may receive your personal information and have access to it in order to comply with legal and regulatory requirements. Your data could be communicated to the abovementioned parties (Medtronic entities or stakeholders only commissioned) in France, in the European Economic Area and the United States, in accordance with the principles of data protection established by the European legislation. Furthermore, the data collected could be examined within the establishment where you are treated by Clinical Research Associates commissioned by Medtronic to verify your medical record. This verification will be confidential and conducted only in the presence of the physician participating in the study.

All stakeholders involved in the study are bound by the obligation of professional or medical secrecy. The information that you provide is confidential. This information will be combined with those of the other patients participating in this study. They will be collected for medical research purposes, in order to gather information on the device and its performance during the study. The study data will be used namely to make a reimbursement request for the system of sacral neuromodulation Interstim® to the HAS. The statistical results of this study may also be presented at meetings or conferences and possibly published. However, your identity will never be revealed during these presentations.

b. Regarding the personal data sent to the call center:

Your name and telephone numbers will be given, only after obtaining your consent, to an external organization which will offer the services of a call center. The only purpose of this call center will be to call you three weeks before each visit to remind you of the date of the visit and the completed documents that you should bring back with you to the visit (i.e. the bowel diary and the quality of life questionnaire).

At the end of the study, your personal data will be destroyed.

**Regulatory aspects**

Your personal data will undergo computer processing. Also, you can exercise your right to access and amend your information at any time during the entire study by contacting your physician, in accordance with the French Law on Information Technology, Data Files and Civil Liberty of January 6, 1978.

You are free to decide whether to agree or refuse to take part in the study, and you can change your mind at any time, without having to state the reason. Your decision to withdraw from the study will
not adversely affect the quality of the medical care that you are entitled to receive or the quality of your relationship with your physician. Your participation in this study will not lead to additional medical costs.

This study is performed in accordance with the applicable regulations, namely the provisions contained in Book 1 Titles 1 and 2 of the Public Health Code and the articles R.5212-1 and the following in the same Code, for the rights of patients in the context of research and medical evaluations. The data transmission procedures are consistent with the European legislation (Directive 95/46/EC of October 24, 1995) and have been declared to the Commission nationale de l'informatique et des libertés (CNIL, National Commission on Informatics and Liberty).

Finally, pursuant to article L4113-6 of the Public Health Code, this study has also been submitted for approval by the Conseil National de l'Ordre des Médecins (National Council of the French Medical Association).

Any questions?

If you have a problem, or you wish to consult a physician, Doctor/Professor ________________________________, telephone no.: __________________________ will be happy to answer your questions on the study entitled Post-Approval Follow-up Study on Sacral Neuromodulation for the Treatment of Fecal Incontinence.
Non-opposition of the conduct of the study entitled
Post-Approval Follow-up Study on Sacral Neuromodulation
for the Treatment of Fecal Incontinence

by Mrs/M. (Last name, first name) ____________________________________________

Doctor/Professor ______________________________________ invited me to participate in the
observational follow-up study of the patients treated by sacral neuromodulation for fecal
incontinence sponsored by the company MEDTRONIC International Trading Sàrl.

He clearly explained that I am free to accept or refuse.

- I have received, and understand clearly, the information presented in the document entitled
  “Patient Data Release Form” regarding the objectives and conditions of the study, as well as the
  type of information that will be collected and how it will be used.

- I am not opposed to the conduct of this study under the conditions stipulated in the “Patient
  Data Release Form”.

- My consent does not exonerate the organizers from their responsibilities. I preserve all my legal
  rights.

- I accept that the data recorded during this study will undergo computer processing by or for the
  sponsor, with the understanding that my name will not appear on any of the files or other
  documents.

- Furthermore, I was informed of the possibility to withdraw my participation to the study at any
  time, regardless of the reason, without having to justify my decision, and without adverse effect
  on the quality of care that I am entitled to receive.

Preparation of two copies:

One copy of the “Patient Data Release Form” and the “Non-opposition to the Conduct of the Study
Form” were given to me. The second copy of the “Patient Data Release Form” and the “Non-
opposition to the Conduct of the Study Form” is maintained in a confidential manner by my
physician.

The patient:

Last name: ____________________________  First name: ____________________________
Signature: ____________________________ Date ____________________________

The investigator:

Last name: ____________________________  First name: ____________________________
Signature: ____________________________ Date ____________________________

Medtronic Confidential
Appendix 2 – List of the Medtronic personnel involved in the study

The composition of the team can be modified during the study. For this reason, possible regular updates will be sent to the study sites separately.
Appendix 3 – List of the sites participating in the study

The list of sites participating in the study, as well as possible updates, will be provided to the investigators separately.
Appendix 4 – Example of Case Report Forms

For this study, the CRFs listed in Table 1 have been developed. A copy of the CRFs developed will be provided to the investigators separately.

The electronic data collection system allows customization of the display and access to the CRFs, or to part of the CRFs, depending on the user profile. Table 1 shows the different types of access rights depending on the CRFs.

Table 1. List of CRFs and user access rights.

<table>
<thead>
<tr>
<th>CRF</th>
<th>Access rights by:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Study site</td>
</tr>
<tr>
<td>Study inclusion</td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td></td>
</tr>
<tr>
<td>Test</td>
<td></td>
</tr>
<tr>
<td>Permanent</td>
<td></td>
</tr>
<tr>
<td>Follow-up visit</td>
<td></td>
</tr>
<tr>
<td>Adverse events</td>
<td></td>
</tr>
<tr>
<td>Study withdrawal</td>
<td></td>
</tr>
<tr>
<td>Modification of the implanted system</td>
<td></td>
</tr>
<tr>
<td>Protocol deviation</td>
<td></td>
</tr>
<tr>
<td>Death of the patient</td>
<td></td>
</tr>
<tr>
<td>Patient’s personal data</td>
<td></td>
</tr>
<tr>
<td>Modification of the telephone numbers</td>
<td></td>
</tr>
<tr>
<td>Schedule of the Follow-up visits</td>
<td></td>
</tr>
</tbody>
</table>

Legend:

- No access right (to examine or modify)
- The right to examine the data of all study sites;
- The right to insert, modify, validate or examine data of his/her own study site
Appendix 5 – Copy of the Clinical Trial Agreement

A copy of the Clinical Trial Agreement will be provided separately to the study sites.
# LIST OF ABBREVIATIONS AND ACRONYMS

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>CRF</td>
<td>Case Report Form</td>
</tr>
<tr>
<td>eCRF</td>
<td>electronic Case Report Form</td>
</tr>
<tr>
<td>FIQL</td>
<td>Fecal Incontinence Quality of Life</td>
</tr>
<tr>
<td>HAS</td>
<td>French National Authority for Health (Haute Autorité de la Santé)</td>
</tr>
<tr>
<td>PP</td>
<td>Primary Population</td>
</tr>
<tr>
<td>SP</td>
<td>Secondary Population</td>
</tr>
<tr>
<td>DTL</td>
<td>Delegated Task List</td>
</tr>
<tr>
<td>CV</td>
<td>Curriculum Vitae</td>
</tr>
<tr>
<td>CCTIRS</td>
<td>Advisory Committee on the Treatment of Information Related to Health Research (Comité consultatif sur le traitement de l'information en matière de recherche dans le domaine de la santé)</td>
</tr>
<tr>
<td>CNIL</td>
<td>National Commission on Informatics and Liberty (Commission nationale de l'informatique et des libertés)</td>
</tr>
<tr>
<td>CNOM</td>
<td>French National Medical Council (Commission nationale de l'informatique et des libertés)</td>
</tr>
<tr>
<td>CRO</td>
<td>Contract Research Organization</td>
</tr>
<tr>
<td>ADELF</td>
<td>Association of French-speaking Epidemiologists (Association Des Epidémiologistes de Langue Française)</td>
</tr>
<tr>
<td>ADEREST</td>
<td>Association for the Development of Epidemiological Studies and Research on Workplace Health (Association pour le Développement des Études et Recherches Épidémiologiques en Santé Travail)</td>
</tr>
<tr>
<td>EPITER</td>
<td>Association for the Development of Field Epidemiology (Association pour le développement de l’épidemiologie de terrain)</td>
</tr>
<tr>
<td>EDC</td>
<td>Electronic data capture</td>
</tr>
<tr>
<td>AE</td>
<td>Adverse events</td>
</tr>
<tr>
<td>ADE</td>
<td>Adverse device effect</td>
</tr>
<tr>
<td>SAE</td>
<td>Serious adverse event</td>
</tr>
<tr>
<td>SADE</td>
<td>Serious adverse device effect</td>
</tr>
<tr>
<td>LOCF</td>
<td>Last observation carried forward</td>
</tr>
<tr>
<td>ISF</td>
<td>Investigator Site File</td>
</tr>
</tbody>
</table>