BDYNCLIN STUDY

10/04/2020

V2-0 PROTOCOL

"Study of the efficacy and tolerance of the B-Dyn medical device compared to a conventional bolted fusion with or without cage in the treatment of degenerative lumbar stenosis, with or without grade I spondylolisthesis on the degree of postoperative functional disability, preservation of mobility and prevention of the adjacent syndrome".

Interventional, prospective, comparative, randomized, non-inferiority, single blind, international, multicenter clinical study.

Document approved for broadcasting : 10/04/2020	By : Docteur O. ZOURABICHVILI President	Visa :
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PROTOCOL NUMBER	3001_BDYNCLIN
DATE	10/04/2020
AUTHORS	Pr Vincent POINTILLART (CHU Bordeaux), Dr Bertrand DEBONO (Clinique des Cèdres) Dr Othar ZOURABICHVILI (QUANTA MEDICAL) Rym BOULKEDID (QUANTA MEDICAL)

Confidential Release

PROTOCOL

"Study of the efficacy and tolerance of the B-Dyn medical device compared to a conventional bolted fusion with or without cage in the treatment of degenerative lumbar stenosis, with or without grade I spondylolisthesis on the degree of postoperative functional disability, preservation of mobility and prevention of the adjacent syndrome".

*Interventional, prospective, comparative, randomized, non-inferiority, single blind, international, multicenter clinical study***.**

Proponent Reference :3001_BDYNCLIN

N° ID RCB : 2020-A00553-36

Indication: degenerative lumbar spinal stenosis

Phase : III

ICH / GCP Declaration: This study will be conducted in accordance with the ICH/GCP and the NF EN ISO-14155 May 2012 norms, specifically on clinical investigations regarding the medical devices in human subjects, and the revision 3 MEDDEV 2.7/3 (May 2015) on SAE reporting.

The research has received a favorable opinion from the Ethical committee XXXXX on the.

COORDINNATING INVESTIGATOR (Orthopaedics)	**COORDINNATING INVESTIGATOR (Neurosurgery)**
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PROPONENT	**MONITOR**
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1. ABBREVIATIONS – DEFINITIONS

1.1. ABBREVIATIONS

CA	Competent Authority
CRA	Clinical Research Associate
ASD	Adjacent Segment Disease
GCP	Good clinical practice
PPC	Protection to Persons Committee
CRF	Case Report Form
CRO	Contract Research Organisation
UE	Undesirable Effect/ Side Effect
SAR	Serious Adverse Reaction
RRQ	Recording Reguarding the Quality
Aes	Adverse Event
SAE	Serious Adverse Event
ICH E3	International Conference on Harmonization E3
ICH E6	International Conference on Harmonization E6
ITT	Intent to Treat
OR	Odds Ratio
PP	Per Protocol
PV	Pharmacovigilance
LSS	Lumbar Spinal Stenosis

1.2. DEFINITIONS

NA.

2. ADDRESSES AND RESPONSIBILITIES

2.1. PROTOCOL SIGNATORIES

The signatories attest that the protocol, the CRF and the annexes contain the information and recommendations necessary to perform this study. The study will be performed and recorded in accordance with this protocol. All legal obligations will be met, as described below.
The signatories agree to conduct the study in accordance with the requirements of the protocol and of GCP/ICH. All changes to the protocol must be approved by the signatories and recorded in writing.
By signing this protocol, the coordinating investigator agrees to allow all persons delegated by Cousin Biotech (auditor, monitors, etc.), or by the Competent Authority (from France or other countries), access to all study data.

SPONSOR
COUSIN BIOTECH
François HENIN, Directeur Général
Allée des Roses
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10/04/2020

Date | Signature

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Date | Signature

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92500 RUEIL-MALMAISON
France

10/04/2020

Date | Signature

2.2. PROTOCOL SIGNATURE PAGE

I have read this protocol and certify that I comply with and will observe the confidentiality of all aspects of the study requirements defined in this document, in the case report form (CRF) and in the other study documents.
I have noted the fact that any failure to meet the study requirements by the investigator (myself) or any member of the investigating team without discussing this in advance with the sponsor or his/her representative (CRO) will be deemed to be a breach of protocol.
I agree to conduct this study in accordance with current regulations, legislation and other requirements, and more specifically:

- Law no. 2012-300 of 5 March 2012 on research involving human beings (the so-called Jardé law) modified by Order no. 2016-800 of 16 June 2016 and Decree no. 2016-1537 through which this law is applied;
- MEDDEV 2.7/3 revision 3 (May 2015) – Guidelines on the reporting of serious adverse events in clinical studies on medical devices:
- The Decision of 3 March 2017 setting out the form, content and methods for declaring adverse events and new findings in research, as described in section 1 of article L. 1121-1 of the French Code of Public Health (CSP) on an MD/IVDMD;
- The French Code of Public Health;
- The Declaration of Helsinki (latest version: October 2013);
- Good Clinical Practice (GCP);
- ICH (International Conference on Harmonization) recommendations and in particular ICH E6 (Good Clinical Practice);
- The law relating to data processing, files and freedoms (law n ° 78-17 amended in 2004)
- Deliberation no. 2018-153 of 3 May 2018 approving a reference methodology for the processing of personal data used in health research with recording of consent from the person concerned (MR-002) and rescinding deliberation no. 2016-262 of 21 July 2016;
- Law 2018-493 of 20 June 2018 on the protection of personal data;
- Standard NF EN ISO 14155 (May 2012) on clinical investigations on medical devices in human subjects.

I have duly noted that the study has been granted:

- A favourable opinion by the Ethics Committee;
- Recording by the Competent Authority.

By the present signature, I authorise access to the study data concerning the patients involved to Cousin Biotech (or to any person duly designated by Cousin Biotech) or to the Competent Authority, etc.).

INVESTIGATOR:

NAME:

Date Signature

3. SYNOPSIS

SYNOPSIS

BDYNCLIN STUDY

05/03/2020

Document approuvé pour diffusion le : 05/03/2020	Par : Docteur O. ZOURABICHVILI Président	Visa :
V:\COUSIN_BIOTECH\COU_BDYNCLIN_19_3001\2-DOC_REFERENT\3-SYNOPSIS\3001_BDYNCLIN_02-03-A-A_SYNOPSIS_200305_V3-0.DOCX		

TITLE	**"Study of the efficacy and tolerance of the B-Dyn medical device compared to a conventional bolted fusion with or without cage in the treatment of degenerative lumbar stenosis, with or without grade I spondylolisthesis on the degree of postoperative functional disability, preservation of mobility and prevention of the adjacent syndrome".** *Interventional, prospective, comparative, randomized, non-inferiority, single blind, international, multicenter clinical study*.
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SPONSOR	COUSIN BIOTECH
MEDICAL DEVICE	B-Dyn ™
DATE AND VERSION	05/03/2020 – V3-0
TITLE	**"Study of the efficacy and tolerance of the B-Dyn medical device compared to a conventional bolted fusion with or without cage in the treatment of degenerative lumbar stenosis, with or without grade I spondylolisthesis on the degree of postoperative functional disability, preservation of mobility and prevention of the adjacent syndrome".** *Interventional, prospective, comparative, randomized, non-inferiority, single blind, international, multicenter clinical study***.**
COORDINATORS	Pr. Vincent POINTILLART Service de Chirurgie orthopédique et traumatologique Unité de Chirurgie du Rachis CHU de Bordeaux – Le Tripode – GH Pellegrin Place Amélie Raba-Léon 33000 BORDEAUX Dr Bertrand Debono Neurochirurgie - Pôle de Neurosciences Clinique des Cèdres - Bat. 2 31700 Cornebarrieu
RATIONAL	The Lumbar Spinal Stenosis: LSS is an extremely common pathology that affects more than 102 million people worldwide every year [1]. It is most often linked to the combination of a disk space narrowing (loss of height and bulging within the canal), a hypertrophy of the yellow ligament and of the joint capsules and also a bone overgrowth by the posterior vertebral joints. This may be associated with Grade I spondylolisthesis. This pathology often extends over several levels, frequently two (L5S1, L4L5 or L4L5, L3L4) sometimes more. A relatively homogeneous group of patients falls within the group of stenosis, from S1 to L2, without significant deviation (scoliosis or cyphosis type). A wide variety of different surgical techniques are used to treat patients with LSS and patients who have symptoms despite well-conducted medical treatment. Decompressive laminectomy may prove to be insufficient when several levels are affected and also due to the fears of instability induced by the gesture itself (the joint hypertrophy responsible for nerve root compression is also a stabilizing element). Therefore, the scientific community usually associates a gesture of stabilization with the gesture of decompression. The choice of stabilizing means is discussed without any conclusive answer provided by any controlled study. This question accounts for the subject of this study. Two alternatives are discussed: • The current gold standard is to practice rigid stabilization through bolted fusion, with or without inter somatic cage, despite the fact that it causes an excessive rigidification of the mobile segment, therefore responsible for the acceleration of the degeneration of the upper level. • Soft stabilization system with pedicular screwing B-Dyn type. It stabilizes the

	arthrodesis while maintaining some mobility. This partial preservation of mobility could slow down or prevent the upper level's degradation. Based on the judgment from the dynamic profile images, the devices, some of which are approved in the USA claim to favor fusion while providing no information on the mobility of the upper level in their studies. The aim of this randomized and prospective comparative study would not only be to establish the non-inferiority of the procedure under study, versus conventional fusion (with or without cage) on the degree of functional disability after surgery, but also to demonstrate the significantly higher preservation of the upper level's mobility when assembling.	
STUDY PERIOD	▪ First inclusion : May 2020 ▪ Inclusion period : 24 months ▪ Last patient's follow up : May 2027 ▪ Analysis and results : November 2027	▪ Phase III
STUDY OBJECTIVES	Primary objective: The main objective is to evaluate at 12 months post-operatively the effect of the B-Dyn device in the treatment of degenerative lumbar stenosis (DLSS), with or without grade I spondylolisthesis compared to classical fusion on the degree of post-operative functional disability. **Secondary objective** 1. To evaluate the effect of B-Dyn in the treatment of DLSS compared to a Classical screw fusion (with or without cage) between inclusion, 2 months, 12 months and 60 months post-intervention on the following: ▪ The mobility of the instrumented level and adjacent levels; ▪ The degree of functional disability related to low back pain; ▪ The lumbar and radicular pain; ▪ The quality of life; ▪ The anxiety; ▪ The radiological parameters; ▪ The neurological and motion status; ▪ The walking distance 2. To evaluate during the study period, the rate of re-operation on the same instrumented level or on the adjacent level. 3. To assess rate of adjacent syndrome (ASD) up to 60 months post intervention 4. To assess side effects reported in both groups.	
ENDPOINTS	**PRIMARY ENDPOINT** The main criterion is the degree of functional disability related to low back pain. It will be measured using the Oswestry Disability Index (ODI) at the 12th month compared to the baseline data. **SECONDARY ENDPOINT**	

	1. the mobility of the instrumented level and adjacent levels will be measured at inclusion, 2 months, 12 months and 60 months post intervention using dynamic X-rays of the lumbar spine: the degree of mobility is calculated by subtracting the angle that is formed in flexure by the tangent of the upper layer of the upper vertebra, and the tangent of the lower layer to the angle formed by these extending tangents. For double instrumentations, an average of the mobility of the two mobile levels is pulled off. 2. the degree of functional disability related to lumbar and radicular pain will be measured by the Oswestry Disability Index (ODI) at inclusion, 2 months, 12 months and 60 months post-intervention; 3. the intensity of radicular and lumbar pain will be assessed by the VAS scale (0-100) at inclusion, 2 months, 12 months and 60 months post-intervention 4. the quality of life will be assessed by the SF-12 score at inclusion, 2 months, 12 months and 60 months post-intervention; 5. anxiety will be measured using the Hospital Anxiety and Depression Scale (HAD) at inclusion, 2 months, 12 months and 60 months post intervention; 6. radiological parameters such as lumbar lordosis (LL), instrumented level segmental lordosis, disk height of the disk above the instrumentation, and pelvic parameters (pelvic incidence PI, Sacral slope (Ps) and pelvic tilt (PT) will be measured at inclusion, 2 months, 12 months and 60 months post intervention using whole body imaging (tele-rachis/ Tele-spine or EOS) 7. Neurological and motion status will be assessed at the instrumented level and adjacent levels (right and left), by measuring motor skills, feeling of touch and stinging sensation at inclusion, 2 months, 12 months and 60 months post-intervention. Various tools will be used: MRC scale (which evaluates motor function from 0: no movement/contractions to 5: normal muscle strength) ; another scale will be used : from 0 (Absent) to 2 (Normal) to evaluate the feeling of touch and sting. 8. The walking distance will be evaluated by self paced test at inclusion, 2 months, 12 months and 60 months post-intervention (patient will walk maximum possible distance) 9. The rate of re-intervention on the instrumented level or adjacent level during the study (up to 60 months). A re-operation during the study is defined as a secondary intervention at the instrumented level or adjacent level for any reason (infectious or mechanical): revision, implant removal (explantation), fusion, need for additional fixation. etc 10. If a patient has one (or more) of the following conditions, he/she is considered to have an adjacent syndrome during the follow-up until the 60th month, ▪ **Adjacent radiological syndrome**: observed from simple and dynamic radiology and from MRI. It is defined by a narrowing of > 3 mm of the disk height, a posterior opening > 5° and sliding progression > 3 mm compared to the pre-operative data of the lateral bending radiology. On the MRI, it is defined by the postoperative progression of disc degeneration according to the Pfirrmann classification, as well as the progression of spinal canal stenosis evaluated according to the classification of Imagama et al [21]. The 1 grade progression of disk degeneration or spinal canal stenosis on

	MRI is considered an adjacent radiological syndrome. ▪ **Adjacent symptomatic syndrome**: is diagnosed when clinical symptoms such as radicular pain or intermittent claudications deteriorate after surgery, and that the lesion responsible for the symptoms is the one adjacent to the fused level (on MRI). ▪ **Surgical Adjacent Syndrome**: is defined as an adjacent symptomatic syndrome, for which surgery is required to treat neurological deterioration at the adjacent degenerative segment. 11. the criteria for assessing safety and tolerance shall be: ▪ The number of patients who experienced at least one adverse event during the follow-up period. ▪ The number of patients who experienced a serious adverse event during the follow-up period, ▪ The short term and long-term, pre-operative and post-operative complications rate
METHODOLOGY	This is a prospective, randomized, multicentric, comparative study of non-inferiority in parallel groups with an allocation ratio of 1:1, single-blind (the patient will be blinded from the arm of randomization), single blind (The patient will be blinded regarding randomization arm). The secondary objective of this study will be to assess the performance of the B-Dyn device compared to a simple fusion on dynamic parameters and the prevention of adjacent syndrome. Randomization, with a ratio of 1:1 will be stratified on the center and on the presence of spondylolisthesis (spondylolisthesis grade 1 on the highest level VS spondylolisthesis grade 1 on the other levels, or no spondylolisthesis at all)
EXPERIMENTAL GROUP	B-Dyn, Medicla device CE Marked
CONTROL GROUP	The bolted fusion technique with or without cage
NUMBER OF PATIENTS REQUIRED	The objective of the project is to look for a non-inferiority of the «B-DYN» group compared to the «bolted fusion with or without cage» group, on the degree of functional disability after surgery evaluated by the Oswestry disability index (ODI) at the 12th month post-surgery. According to the literature, patients with a fusion shows 37.1% ODI decrease by 1-year, compared to the baseline. Considering this hypothesis, a sample size of N= 188 patients (94 “Bdyn” / 94 “Fusion”) will be a 90% demonstration proof of a non-inferiority by considering a non-inferiority margin of -2 and a standard deviation of 6.7. Considering a 15% attrition rate, we will include a total of 216 patients. An interim analysis is planned once 100 patients will have reached the main assessment criterion.
INCLUSION CRITERIA	**Disease related criteria:** 1. Stenosis on 1 or 2 adjacent segments (grade C or D according to Schizas classification) on MRI 2. Spondylolisthesis grade 1 or no spondylolisthesis 3. Pseudoclaudication (Pseudoclamping) on one or both legs and back pain (VAS score> 30)

	4. Patient who has failed well-managed medical treatment that has not resulted in long-lasting symptom relief (duration of symptoms > 6 months); 5. Patient with no contraindication to fusion or the application of B-Dyn®. **Population-related criteria** 1. Subject: both sexes, 40 years of age and older 2. Patient who has given free, informed and written consent to participate in the study; 3. Patient who is able to respond to questionnaires and who can communicate in the language of the study country ; 4. Patient affiliated to a social security scheme or entitled to a social security scheme.
NON INCLUSION CRITERIA	**Disease related criteria**: 1. Spondylolisthesis of grade > 1 2. Degenerative Scoliosis (Cobb angle > 20°); 3. History of fusion for spinal stenosis or vertebral instability 4. Stenosis not caused by from degenerative changes. 5. Isolated disc herniation 6. Other specific vertebral damage (for example: ankylosing spondylitis, cancer or neurological disorders) 7. History of vertebral fractures resulting from the compression at the instrumented level 8. History of osteoporotic fractures 9. Psychological disorders (e.g. dementia or substance abuse) that lead to an inability to participate in the study 10. Intervention required on more than 3 vertebral levels; 11. Chronic infection **Population related criteria**: 1. Withdrawal of consent; 2. Pregnancy; 3. Breastfeeding woman; 4. Participation in a clinical trial in the 3 months prior to the initial visit; 5. Drug addiction; 6. Predicted unavailability during study. Patient deprived of liberty or under guardianship. **Medical Device related criteria**: 1. Allergy to any of the components of the medical device.
STUDY DESIGN	Patient assessments will be carried out in the following stages: **Visit 1 : Inclusion** 1. Inform the patient and collect his/her informed consent form; 2. Perform a general clinical test; 3. Collect the medical history, the associated pathologies and the surgical history; 4. Note all concomitant treatments; 5. Collect the data base on CRF and will complete or make sure to have the following questionnaires completed: ▪ Questionnaire to calculate the Oswestry Disability Index ; ▪ SF-12 ; ▪ Motion and sensitivity assessment ; ▪ Assessment of lumbar and radicular pain through the VAS

	▪ Assessment of the anxiety through the HAD questionnaire ▪ Assessment of the walking distance 6. Perform an intraoperative lumbar spine MRI for compression objectification and specify the Modic stage 7. Whole Body Imaging (Tele-rachis or EOS) to assess radiological parameters such as Lumbar Lordosis (LL), Instrumented Level Segmental Lordosis (LS), … etc 8. An X-ray examination - dynamic images of the lumbar in flexion/extension and its lateral angulation 9. Verify the inclusion and non-inclusion criteria (to be verified when of all the results are collected); 10. Set the date of intervention 11. The investigator will proceed – immediately or during consultation – to random draw in order to pick the intervention. Therefore, the investigator will log on to Quanta View®, in order to obtain the randomization results. **Visit 2: INTERVENTION AND POST-OPERATIVE FOLLOW-UP** 1. Collect the concomitant treatments; 2. Collect the operative data : ▪ Surgery date ; ▪ Duration of the intervention ; ▪ Installation of the device ; ▪ Adverse events: complications linked to surgery and complications linked to the installation of the implant (for example, insufficient distance between the screws) 3. Collect the immediate post-operative data: ▪ Duration of stay at the hospital; ▪ Pain (VAS) on the post-operative day; 4. Collect the tolerance data and search for adverse events; 5. Complete the CRF for the visit that corresponds; 6. Plan the next visit. **Visit 3 – 2ND MONTH POST-SURGERY (± 7 DAYS),** 1. A clinical test ; 2. Collect the concomitant treatments ; 3. Collect of the intercurrents effects (AEs/SAE) ; 4. Whole-body imaging (Tele-rachis or EOS) to evaluate radiological parameters such as lumbar lordosis (LL), segmental lordosis of instrumented level (LS), etc. etc 5. Radiographic examination of dynamic lumbar images, in flexion/extension and in lateral inclination; this helps to measure the mobility and the search for the material mobilization in relation to the vertebrae (lysis chamber). If such mobilization exists, a scanner will be performed to confirm it. 6. CRF data collection and completion (or make sure to complete) of various questionnaires: ▪ SF-12 ; ▪ Questionnaire to calculate the Oswestry Disability Index; ▪ Motion and sensitivity assessment

	▪ Assessment of the lumbar and radicular pain through the VAS ▪ HAD Questionnaire for anxiety; ▪ Walking distance 7. Collect of surgical re- operations (date, ground, etc.) ; **Visit 4 – 12TH MONTH (D365± 30 DAYS),** 1. A clinical test ; 2. collect concomitant treatmentss ; 3. Collect intercurrents effects (AEs/SAE) ; 4. Whole-body imaging (Tele-rachis or EOS) to evaluate radiological parameters such as lumbar lordosis (LL), segmental lordosis of instrumented level (LS), etc. etc 5. Radiographic examination of dynamic lumbar images, in flexion/extension and in lateral inclination; this helps to measure the mobility and the search for the material mobilization in relation to the vertebrae (lysis chamber). If such mobilization exists, a scanner will be performed to confirm it. 6. An MRI 7. CRF data collection and completion (or make sure to complete) of various questionnaires: ▪ SF-12 ; ▪ Questionnaire to calculate the Oswestry Disability Index; ▪ Motion and sensitivity assessment ▪ Assessment of the lumbar and radicular pain through the VAS ▪ HAD Questionnaire for anxiety; ▪ Walking distance 8. Collect of surgical re-operations (date, ground, etc.) ; **Visit 5 – 60TH MONTH (D365± 30 DAYS**), 1. A clinical test ; 2. collect concomitant treatments ; 3. Collect intercurrents effects (AEs/SAE); 4. Whole-body imaging (Tele-rachis or EOS) to evaluate radiological parameters such as lumbar lordosis (LL), segmental lordosis of instrumented level (LS), etc. 5. Radiographic examination of dynamic lumbar images, in flexion/extension and in lateral inclination; this helps to measure the mobility and the search for the material mobilization in relation to the vertebrae (lysis chamber). If such mobilization exists, a scanner will be performed to confirm it. 6. An MRI 7. CRF data collection and completion (or make sure to complete) of various questionnaires: ▪ SF-12 ; ▪ Questionnaire to calculate the Oswestry Disability Index; ▪ Motion and sensitivity assessment ▪ Assessment of the lumbar and radicular pain through the VAS ▪ HAD Questionnaire for anxiety; ▪ Walking distance 8. CRF data collection and completion (or make sure to complete) of various questionnaires:

	9. Collect of surgical re- operations (date, ground, etc.) ;

4. SCIENTIFIC JUSTIFICATION AND GENERAL DESCRIPTION OF THE RESEARCH

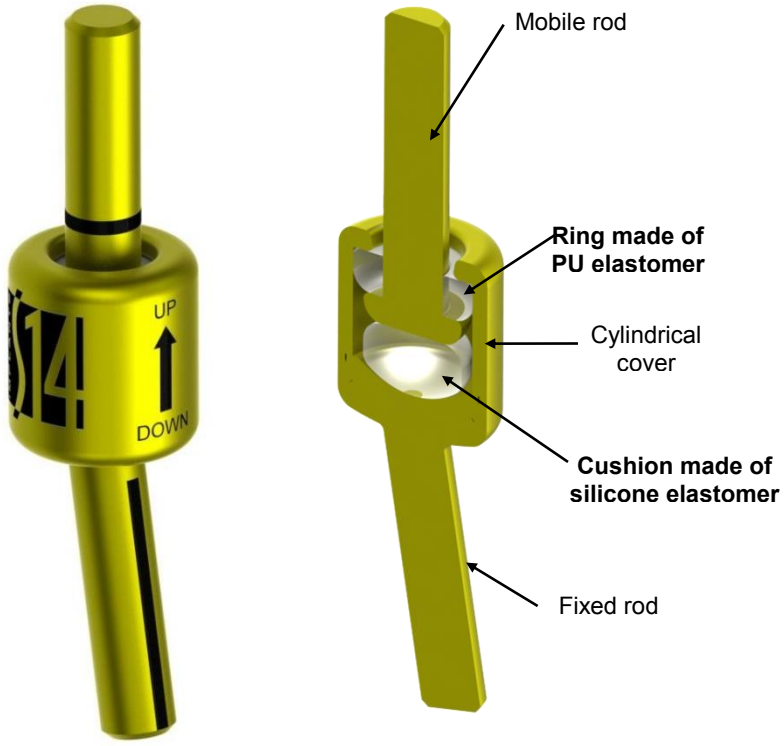
4.1. NAME AND DESCRIPTION OF THE MEDICAL DEVICE TO WHICH THE RESEARCH RELATES

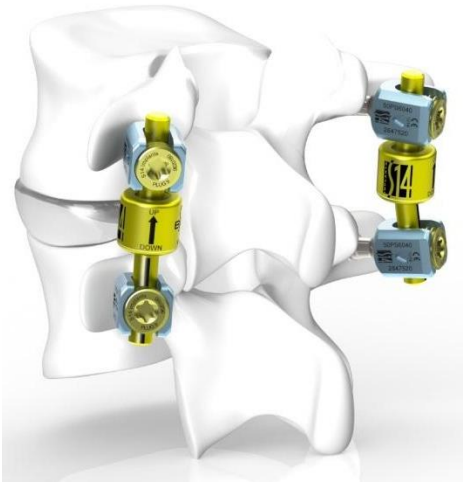
B-Dyn® medical device is a dynamic posterior stabilization system used for the treatment of disc degeneration and/or joint facets, spinal stenosis, grade I spondylolisthesis and segmental hyper-mobility.
The Bdyn spine cushioning with Sterile Posterior Dynamic Stabilization - Bdyn is composed of a hollow metal cylindrical body containing elastomeric silicone and urethane polycarbonate components that are implantable in the long run, and are deformed by a metal piston rod connected to the vertebra of the treated segment by pedicular polyaxials Bdyn screws. The elastomeric components ensure the absorption of the mechanical stresses exerted on the intervertebral joint that are in compression, in traction, in flexion-extension, and in lateral flexion. Some configurations allow the fixation of several intervertebral levels.

The B-Dyn device components as well as their properties are represented in the Figure 1.
The combination of rigid and flexible parts allows to preserve mobility and absorb the bending loads, the traction and the compression.
The B-Dyn product range is available in four different models:

Size of B-Dyn	Small	Medium	Small	Medium
Diameter of rod	5.0 mm	5.0 mm	5.5 mm	5.5 mm
Reference	RCBDYSD50U	RCBDYMD50U	RCBDYSD55U	RCBDYMD55U

The references of the different models of the B Dyn device are listed in Appendix 20.2





A dynamic level

A dynamic level and one (or two) maximum fusion level

The device's detailed description is provided in the instruction manual and in the description of the surgical technique (cf. appendices 20.3 and 20.4)

The B Dyn device belongs to Class IIB. It obtained the CE marking in 2008. The CE conformity assessment was carried out by SGS (see Appendices 20.5). It is used worldwide.

In addition to preserving the mobility of the treated segments, the surgeons appreciate in one hand, the speed of the intervention, and on the other hand, the compatibility of the device with the fusion, which allows them to to choose the best suited system for the patient, during the surgery (this decision is made once the screws are placed, the doctor can choose between fusion or B-Dyn®).

4.2. DESCRIPTION AND JUSTIFICATION OF THE USE OF THE MEDICAL DEVICE AND THE TREATMENT TIME

The Bdyn spine cushioning with Sterile Posterior Dynamic Stabilization- Bdyn is intended for posterior stabilization of the thoracic vertebra T10 at the sacrum S1, with or without bone graft for the following:

- Degeneration of the intervertebral disc and/or joint facets, confirmed by further tests.
- Stenosis of the lumbar canal
- Grade 1 degenerative spondylolisthesis
- Segmental hypermobility

The Bdyn device must be implanted exclusively by a qualified surgeon. The latter needs to have the knowledge of the use of the product as well as the knowledge of anatomy, spine surgery, the technique of attaching the pedicular screws and the specific surgical technique of installing the Bdyn device.

4.3. DETAILED DESCRIPTION OF THE USE OF THE DEVICE TO WHICH THE RESEARCH RELATES AND OF THE SURGICAL PROCEDURES

The surgical technique for the installation of the B-Dyn device is detailed in Appendix 20.3 and 20.4. Surgery is performed under general anesthesia.

The procedure begins with the installation of the first upper polyaxial screw using a polyaxial screwdriver. In order to position the second screw, it is necessary to use the phantom (Trial 10). Once the screws are positioned, the B-Dyn is caught between the jaws of the grip detection, so it can be inserted into the head of the polyaxial screws. The B-Dyn's mobile rod is then placed into the top screw head. The fixed rod's positioning must be placed facing the operator, and it has to be into the center of the lower screw head.

The B-DYN grip detection has to be held first, and then, the clamp adjustment is inserted in order to adjust the inter-pedicular distance of the B-DYN. Finally, the cap of the lower polyaxial pedicular screw is tightened.

A final tightening of the two screw caps on the polyaxial pedicular screws is made for maximum security.

4.4. SCIENTIFIC JUSTIFICATION OF THE RESEARCH

Degenerative lumbar stenosis (Lumbar Spinal Stenosis: LSS) is an extremely common disease affecting more than 102 million people worldwide every year [1].

It is one of the most common indications for spinal surgery [2, 3].

It is the result a degenerative cascade combining a disc pinch (loss of height and bulging in the vertebral canal), a hypertrophy of the ligaments and joint capsules, and a bone hypertrophy in the posterior joints processes. In addition to these stenotic elements, there may be some malalignment of the vertebrae as they may shift from one another (spondylolisthesis grade I), or there may even occur some deformations such as the scoliosis or degenerative cyphosis type. This pathology often develops on a number of levels, frequently two (L5S1, L4L5 or L4L5, L3L4), and sometimes even more. These elements cause a narrowing of the canal containing the spinal nerves, they also cause invertebral foramen allowing the nerves to exit the canal. The clinical symptomatology of this nosological set combines spinal pain and root pain with possibly neurological claudication, degrading patients' quality of life [4].

The therapeutic approach often requires surgery, in cases in which the well-conducted medical treatment remains unsuccessful [5]. Quite a few surgical techniques are used to treat patients with LSS, still, there is much controversy about this multifaceted syndrome [6].

The elementary surgical step (laminectomy) is intended to decompress the contents of the degenerative canal, but it may be insufficient when several levels are affected, and because the means of union between the vertebrae have been sacrificed, this may cause additional instability induced by the gesture itself [5, 7]. This instability can in turn cause painful symptoms of the lower back and/or or of the joints, and impaired neurological signs [8, 9].

Therefore, it has been suggested by many authors to associate a gesture of stabilization with the gesture of decompression [10].

The choice of stabilization means is discussed without any controlled study providing a conclusive response [11–14]. This question is the subject of this study.

Two alternatives were discussed:

- Rigid stabilisations by bolted fusion, with or without inter somatic cage (intersomatic arthrodesis), are the current standard gold, although they are blamed for excessive rigidification of the mobile segment responsible for the acceleration of the degeneration of the upper level (Adjacent Segment Disease: ASD) [8].
- Flexible stabilization systems with dynamic rod and pedicular screwing (for example, type B-Dyn, Dynesys). This allows to stabilize the segment(s) operated while keeping some mobility of the anatomical region. This partial preservation of mobility could slow or prevent the degradation of the upper level [15]

As a matter of fact, the ongoing degeneration of the adjacent segments relative to a lumbar vertebral fusion is a concern for surgeons, and a source of symptoms for patients. This degeneration of the upper level represents a significant percentage of the spinal revision surgery [16]. Literature tells us that radiographic degeneration of the adjacent segment is very common after lumbar spinal fusion (5-45% of cases), but a smaller proportion of this evolution causes clinically significant symptoms, or requires revision surgery (2-15%) [17]. These revision procedures (neurological decompression on the incriminated level, cephalic and/or caudal extension of the assembly) require surgical procedures that can be complex, and may imply significant morbidity risks to patients [18].

Several types of dynamic stabilization devices have been developed to reduce mechanical stress on the adjacent segment. All of them claim the quality of the fusion, however, there are controversies about whether or not, such devices can reduce the ASD [19]. The current state of the art does not allow any conclusion.

The ideal procedure would therefore be to combine a dynamic stabilization with the first step of decompression; this dynamic stabilization provides the patient with the clinical benefits of a fusion without degrading the upper level [20].

Therefore, it seems relevant to be able to provide reliable data on (i) the 12th-month clinical results of this type of implants, when it comes to pain control and quality of life improvement, and also, data on (ii) the radiological parameters showing the preservation of the mobility of the upper level which reflects the protective effect of this dynamic system. The study will be extended by a 60th-month assessment to assess the presence of an adjacent clinical and radiological syndrome.

The objective of this randomized, prospective comparative study would be to establish the non-inferiority of the studied device versus conventional fusion (with or without cage) on the degree of functional incapacity after surgery, but also to demonstrate the preservation of the mobility of the upper level when assembled.

5. OBJECTIVES OF THE STUDY

5.1. MAIN OBJECTIVE

The main objective is to evaluate at 12 months post-operatively the effect of the B-Dyn device in the treatment of degenerative lumbar stenosis (DLSS), with or without grade I spondylolisthesis compared to classical fusion on the degree of post-operative functional disability..

5.2. SECONDARY OBJECTIVES

1. To evaluate the effect of B-Dyn in the treatment of DLSS compared to a Classical screw fusion (with or without cage) between inclusion, 2 months, 12 months and 60 months post-intervention on the following:

    - The mobility of the instrumented level and adjacent levels;
    - The degree of functional disability related to low back pain;
    - The lumbar and radicular pain;
    - The quality of life;
    - The anxiety;
    - The radiological parameters;
    - The neurological and motion status;
    - The walking distance

2. To evaluate during the study period, the rate of re-operation on the same instrumented level or on the adjacent level.
3. To assess rate of adjacent syndrome (ASD) up to 60 months post intervention

4. To assess side effects reported in both groups.

6. STUDY DESIN

6.1. EVALUATION CRITERIA

6.1.1. PRIMARY ENDPOINT

The main criterion is the degree of functional disability related to low back pain. It will be measured using the Oswestry Disability Index (ODI) at the 12th month compared to the baseline data.

6.1.2. SECONDARY ENDPOINTS

1. the mobility of the instrumented level and adjacent levels will be measured at inclusion, 2 months, 12 months and 60 months post intervention using dynamic X-rays of the lumbar spine: the degree of mobility is calculated by subtracting the angle that is formed in flexure by the tangent of the upper layer of the upper vertebra, and the tangent of the lower layer to the angle formed by these extending tangents. For double instrumentations, an average of the mobility of the two mobile levels is pulled off.
2. the degree of functional disability related to lumbar and radicular pain will be measured by the Oswestry Disability Index (ODI) at inclusion, 2 months, 12 months and 60 months post-intervention;
3. the intensity of radicular and lumbar pain will be assessed by the VAS scale (0-100) at inclusion, 2 months, 12 months and 60 months post-intervention
4. the quality of life will be assessed by the SF-12 score at inclusion, 2 months, 12 months and 60 months post-intervention;
5. anxiety will be measured using the Hospital Anxiety and Depression Scale (HAD) at inclusion, 2 months, 12 months and 60 months post intervention;
6. radiological parameters such as lumbar lordosis (LL), instrumented level segmental lordosis, disk height of the disk above the instrumentation, and pelvic parameters (pelvic incidence PI, Sacral slope (Ps) and pelvic tilt (PT) will be measured at inclusion, 2 months, 12 months and 60 months post intervention using whole body imaging (tele-rachis/ Tele-spine or EOS)
7. Neurological and motion status will be assessed at the instrumented level and adjacent levels (right and left), by measuring motor skills, feeling of touch and stinging sensation at inclusion, 2 months, 12 months and 60 months post-intervention. Various tools will be used: MRC scale (which evaluates motor function from 0: no movement/contractions to 5: normal muscle strength) ; another scale will be used : from 0 (Absent) to 2 (Normal) to evaluate the feeling of touch and sting.
8. The walking distance will be evaluated by self paced test at inclusion, 2 months, 12 months and 60 months post-intervention (patient will walk maximum possible distance)
9. The rate of re-intervention on the instrumented level or adjacent level during the study (up to 60 months). A re-operation during the study is defined as a secondary intervention at the instrumented level or adjacent level for any reason (infectious or mechanical): revision, implant removal (explantation), fusion, and need for additional fixation. etc
10. If a patient has one (or more) of the following conditions, he/she is considered to have an adjacent syndrome during the follow-up until the 60th month,

    - **Adjacent radiological syndrome**: observed from simple and dynamic radiology and from MRI. It is defined by a narrowing of > 3 mm of the disk height, a posterior opening > 5° and sliding progression > 3 mm compared to the pre-operative data of the lateral bending radiology. On the MRI, it is defined by the postoperative progression of disc degeneration according to the

Pfirrmann classification, as well as the progression of spinal canal stenosis evaluated according to the classification of Imagama et al [21]. The 1 grade progression of disk degeneration or spinal canal stenosis on MRI is considered an adjacent radiological syndrome.

- **Adjacent symptomatic syndrome**: is diagnosed when clinical symptoms such as radicular pain or intermittent claudications deteriorate after surgery, and that the lesion responsible for the symptoms is the one adjacent to the fused level (on MRI).
- **Surgical Adjacent Syndrome**: is defined as an adjacent symptomatic syndrome, for which surgery is required to treat neurological deterioration at the adjacent degenerative segment.

11. the criteria for assessing safety and tolerance shall be:

- The number of patients who experienced at least one adverse event during the follow-up period.
- The number of patients who experienced a serious adverse event during the follow-up period,
- The short term and long-term, pre-operative and post-operative complications rate

6.2. RESEARCH METHODOLOGY

6.2.1. STUDY DESIGN AND FLOW CHART

This is a prospective, randomized, multicenter, comparative study of non-inferiority in parallel groups with an allocation ratio of 1:1, single-blind (the patient will be blinded from the arm of randomization).

The duration of patient follow-up is 60 months. The inclusion period is 24 months in order to recruit the number of subjects needed for the study.

When the patient is eligible, he is randomized. After each procedure, the follow-up is scheduled over 60 months, with 3 consultation visits scheduled after surgery: in the 2nd, 12th and 60th months, with collection and measurement of the criteria for evaluation.

The *V1 Inclusion Visit* will confirm the indication; the inclusion and non-inclusion criteria will be assessed; the patient will have the opportunity to sign the consent. The random draw is also done during this visit (before the surgery).

The *Visit V2* corresponds to the procedure. The *Visit V3* happens at the 2nd month following the surgery. The *Visit V3* on the 12th month will help assess the main judgement criterion, and the one that happens on the 60th month (V5) as the study closes

In case of hospitalization or consultation that occurs outside the original schedule, additional visits will be planned

Visits	V1 Inclusion	V2 intra- & post-op	V3 Follow up	V4 Follow up	V5 Follow up	Additional visits
Days Data to be collected or Tests to be done		D0	M2 (± 7 d)	M12 (± 30 d)	M60 (± 60 d)	Consultation or hospitalisation
Information and signature of the consent	✓					
Medical history	✓					
History of the disease	✓					
Inclusion / non-inclusion criteria	✓					
Clinical test	✓	✓	✓	✓	✓	✓
Randomization and allocation of intervention	✓					
Intra-post-op. Immediat data collection		✓				
Case Report Form (CRF)	✓	✓	✓	✓	✓	✓
Oswestry Disability Index	✓		✓	✓	✓ (sup)	✓
Quality of life questionnaire (SF-12)	✓ (sup)		✓ (sup)	✓ (sup)	✓ (sup)	
Motion and sensitivity assessment	✓		✓	✓	✓ (sup)	
VAS (low back pain and radicular pain)	✓	✓	✓	✓	✓ (sup)	
Anxiety (HAD score)	✓ (sup)		✓ (sup)	✓ (sup)	✓ (sup)	
Walking distance	✓		✓	✓	✓ (sup)	
MRI	✓			✓ (sup)	✓ (sup)	
Radiography (Télé-rachis or EOS)	✓		✓	✓	✓ (sup)	
Dynamic Radiograph	✓		✓	✓	✓ (sup)	✓
AE (Adverse event) collection		✓	✓	✓	✓	✓
Collect of concomitant treatments		✓	✓	✓	✓	✓

Supp : Additional tests compared to common practices

6.2.2. PARTICIPATION SITES

The research will be carried out in the following countries: France, Belgium, Georgia, with 20 participating centers.

Each center will have to recruit an average of 12 to 18 patients.

The centers were selected according to the following criteria:

- Ability to recruit patients according to protocol;
- Sufficient availability to conduct the study;
- Ability to obtain high quality data in accordance with protocol requirements;
- Adherence to regulatory requirements (BPC, etc.), legal requirements and other requirements that are specific to the study.

In addition, investigators must meet the following criteria:

- Have recognized experience in surgical treatment of degenerative lumbar stenosis and rod placement.

6.3. MEASURES TAKEN TO REDUCE AND AVOID BIAS

6.3.1. RANDOMIZATION

This is a randomized study. The randomization list will be generated using SAS® 9.4 software. Once the eligibility criteria have been verified and once the consent have been obtained, the patient will be randomized by the computer. Randomization, with a ratio of 1:1 will be stratified on the center and on the presence of spondylolisthesis (spondylolisthesis grade 1 on the highest level VS spondylolisthesis grade 1 on the other levels, or no spondylolisthesis at all). Randomization is performed in blocks of random sizes. It will be performed via the electronic application QUANTA VIEW®.

During each randomization, electronic information will be sent to the member of the study team responsible for monitoring inclusion rates. This information will include the patient's initials, the date of inclusion, the inclusion number for the study, and the identification of the physician who included the patient.

6.3.2. BLINDING

The patient will be blinded to randomization arm. Since the procedure is performed under general anesthesia, the patient will not be informed whether or not the B-Dyn® device has been installed during the procedure. The assessment of the main judgement criterion (the ODI being a patient reported outcome) will therefore be blind to the group of randomization. Other secondary criteria such as quality of life or pain intensity will also be evaluated blindly in regards to the group of randomization (assessment by patient). The blind process cannot be applied to the surgeon. The installation of the device cannot be hidden from him or her.

A centralized reading of all radiographs (Tele-rachis or dynamic images) will be performed by an independent radiologist.

The assessment criteria such as the re- operations are objective criteria, and they can be assessed without bias even if the monitor has some knowledge of the group randomization.

6.3.3. BLIND REVIEW

The data review will be carried out at the end of the study to judge deviations. It will be done by the steering committee, blind to the group of randomization.

6.4. MODALITIES FOR USING THE DEVICES ON WHICH THE RESEARCH IS RELATED AND THE SURGICAL PROCEDURES INVOLVED IN THE IMPLEMENTATION OF THE DEVICE IN THE RESEARCH

6.4.1. THE B-DYN® DEVICE

All the investigators performing this implant must be surgeons who has a broad experience in the installation of surgical treatment devices for degenerative lumbar stenosis.

The contents of the devices used for the research are aseptically-packaged. The implantation instruments, supplied separately for B-DYN are not sterile and must be sterilized beforehand (See details in appendix 20.2).

The B-DYN® device is described in paragraph 4.1. The surgical installation technique is developed in the attached manual (Appendix 20.5).

The procedure is performed under general anesthesia.

6.4.2. THE BOLTED FUSION TECHNIQUE WITH OR WITHOUT CAGE

The fusion, also called lumbar arthrodesis consists of blocking the painful level(s), in order to limit the movement of the affected disc. In just few months, this assembly results in the fusion (or welding) of the affected vertebrae, and therefore decreases the pain. The surgeon will complete his gesture by placing 2 screws in the upper vertebra and 2 screws in the lower vertebra; the screws will be connected to each other to stabilize the assembly. This type of surgery is done via posterior approach.

6.5. PROCESS AND DURATION OF INDIVIDUALS PARTICIPATION

6.5.1. PROCESS FOR A PATIENT

6.5.1.1. *VISITS V1 – INCLUSION VISIT*

During the visit, the investigator will:

1. Inform the patient and collect his/her informed consent form;
2. Perform a general clinical test;
3. Collect the medical history, the associated pathologies and the surgical history;
4. Note all concomitant treatments;
5. Collect the data base on CRF and will complete or make sure to have the following questionnaires completed:
    - Questionnaire to calculate the Oswestry Disability Index ;
    - SF-12 ;
    - Motion and sensitivity assessment ;
    - Assessment of lumbar and radicular pain through the VAS
    - Assessment of the anxiety through the HAD questionnaire
    - Assessment of the walking distance
6. Perform an intraoperative lumbar spine MRI for compression objectification and specify the Modic stage
7. Whole Body Imaging (Tele-rachis or EOS) to assess radiological parameters such as Lumbar Lordosis (LL), Instrumented Level Segmental Lordosis (LS), … etc
8. An X-ray examination - dynamic images of the lumbar in flexion/extension and its lateral angulation

9. Verify the inclusion and non-inclusion criteria (to be verified when of all the results are collected);
10. Set the date of intervention
11. The investigator will proceed – immediately or during consultation – to random draw in order to pick the intervention. Therefore, the investigator will log on to Quanta View®, in order to obtain the randomization results.

After reviewing that the eligibility criteria are met, that the patient is absolutely clear in terms of the consent he/she is giving, the investigator will proceed - immediately or during the consultation - to the random draw in order to pick the intervention. Therefore, the investigator will log on to QUANTA VIEW® to retrieve randomization results. The patient will then be assigned an anonymity number (this will later reported as the patient identifier).

The patients will belong to either one of the following :

1. The « B-Dyn» arm;
2. The Fusion arm : with or without a cage

6.5.1.2. *VISIT V2 – INTERVENTION AND POST-OPERATIVE FOLLOW-UP*

During the intervention, the investigator will:

1. Collect the concomitant treatments;
2. Collect the operative data :
    - Surgery date ;
    - Duration of the intervention ;
    - Installation of the device ;
    - Adverse events: complications linked to surgery and complications linked to the installation of the implant (for example, insufficient distance between the screws)
3. Collect the immediate post-operative data:
    - Duration of stay at the hospital;
    - Pain (VAS) on the post-operative day;
4. Collect the tolerance data and search for adverse events;
5. Complete the CRF for the visit that corresponds;
6. Plan the next visit.

6.5.1.3. *VISIT V3 –2ND MONTH POST-SURGERY (± 7 DAYS),*

This visit occurs on the 2nd month post-surgery. It will include :

1. A clinical test ;
2. Collect the concomitant treatments ;
3. Collect of the intercurrents effects (AEs/SAE) ;
4. Whole-body imaging (Tele-rachis or EOS) to evaluate radiological parameters such as lumbar lordosis (LL), segmental lordosis of instrumented level (LS), etc. etc
5. Radiographic examination of dynamic lumbar images, in flexion/extension and in lateral inclination; this helps to measure the mobility and the search for the material mobilization in relation to the vertebrae (lysis chamber). If such mobilization exists, a scanner will be performed to confirm it.
6. CRF data collection and completion (or make sure to complete) of various questionnaires:
    - SF-12 ;
    - Questionnaire to calculate the Oswestry Disability Index;
    - Motion and sensitivity assessment
    - Assessment of the lumbar and radicular pain through the VAS
    - HAD Questionnaire for anxiety;
    - Walking distance
7. Collect of surgical re- operations (date, ground, etc.) ;

6.5.1.4. *VISIT V4 – 12TH MONTH (D365± 30 DAYS),*

The visit will occur on the 12th month, $D_{365} \pm 30$ days. It will include :

1. A clinical test ;
2. collect concomitant treatmentss ;
3. Collect intercurrents effects (AEs/SAE) ;
4. Whole-body imaging (Tele-rachis or EOS) to evaluate radiological parameters such as lumbar lordosis (LL), segmental lordosis of instrumented level (LS), etc. etc
5. Radiographic examination of dynamic lumbar images, in flexion/extension and in lateral inclination; this helps to measure the mobility and the search for the material mobilization in relation to the vertebrae (lysis chamber). If such mobilization exists, a scanner will be performed to confirm it.
6. An MRI
7. CRF data collection and completion (or make sure to complete) of various questionnaires:
    - SF-12 ;
    - Questionnaire to calculate the Oswestry Disability Index;
    - Motion and sensitivity assessment
    - Assessment of the lumbar and radicular pain through the VAS
    - HAD Questionnaire for anxiety;
    - Walking distance
8. Collect of surgical re-operations (date, ground, etc.) ;

6.5.1.5. *VISIT V5 – 60TH MONTH (D365± 30 DAYS),*

The visit will occur on the 60th month, $D_{1825} \pm 30$ days. It will include:

1. A clinical test ;
2. collect concomitant treatments ;
3. Collect intercurrents effects (AEs/SAE);
4. Whole-body imaging (Tele-rachis or EOS) to evaluate radiological parameters such as lumbar lordosis (LL), segmental lordosis of instrumented level (LS), etc.
5. Radiographic examination of dynamic lumbar images, in flexion/extension and in lateral inclination; this helps to measure the mobility and the search for the material mobilization in relation to the vertebrae (lysis chamber). If such mobilization exists, a scanner will be performed to confirm it.
6. An MRI
7. CRF data collection and completion (or make sure to complete) of various questionnaires:
    - SF-12 ;
    - Questionnaire to calculate the Oswestry Disability Index;
    - Motion and sensitivity assessment
    - Assessment of the lumbar and radicular pain through the VAS
    - HAD Questionnaire for anxiety;
    - Walking distance
8. CRF data collection and completion (or make sure to complete) of various questionnaires:
9. Collect of surgical re- operations (date, ground, etc.) ;

6.5.1.6. *ADDITIONAL VISIT OR HOSPITALIZATION*

In the case of an unplanned visit or in the case of hospitalization, a visit will be planned.

6.5.2. EXAMINATIONS THAT ARE NOT COMMON PRACTICES

Patients are usually consulted by the 2nd and 12th month post-surgery. The tests performed during these visits are the common tests: x-rays, MRI … etc. The questionnaires to assess the quality of Life, the ODI, the Neurological and Motor Status are also performed during the patient's usual care. The MRI costs for the 12th month visit will be covered by the sponsor as part of this research.

The 60th-month visit is added to the usual patient care. The costs of the 60th month visit tests (MRI, X-rays, travel expenses) will be borne by the sponsor as part of this research.

6.6. DESCRIPTION OF RULES FOR TEMPORARILY OR PERMANENTLY STOPPING THE STUDY

6.6.1. PATIENT DROP OUTS

The patient may withdraw from the study at any time on the decision of the investigator or on the patient's own decision because of:

- Withdrawal of consent;
- Inability to continue the protocol;
- Explantation of the device ;
- Etc.

Regardless of the reason for premature withdrawal, the investigator must complete the end of study assessment in the CRF. The main reason for study withdrawal will be documented in the source file and in the CRF.

For patients lost to follow-up, the investigator must indicate in the source file the reason for study withdrawal (loss to follow-up) and indicate details of reminder telephone calls/letters to the patient asking him to return for the final evaluation visit.

6.6.2. STUDY TERMINATION BY DECISION OF THE SPONSOR

There are no specific rules governing discontinuation of the study by the sponsor. The latter thus reserves the right to terminate the study at any time. If the sponsor terminates the biomedical study early or suspends it temporarily, the investigator will be informed immediately of the reason for such termination or suspension closure of a study centre.

6.6.3. CENTER CLOSURE

An investigating centre may be closed:

- On the decision of the sponsor in the event of:
  - Lack of inclusions within 3 months after the study set-up date;
  - Non-compliance with GCP/ICH in conducting the study.
- On the decision of the investigator. In this case, the investigator will inform the sponsor as soon as possible and explain the reasons for discontinuing the study in detail in writing.

6.6.4. PATIENT FOLLOW-UP PROCEDURES IN THE EVENT OF TERMINATION

If the devices are explanted or the patient withdraws his/her consent, his/her clinical follow-up is continued outside of the protocol according to the patient's usual management until the end of the follow-up period stipulated in the

study. The same applies if the study is stopped. If the B-DYN is explanted the patient may be offered implantation of an alternative device such as intersomatic cages… etc or a fusion

Patients will continue to be followed-up in their original department regardless of the reasons for discontinuation of the study.

6.7. ACCOUNTABILITY PROCEDURES

The devices will be packaged by the Sponsor, in compliance with legal and regulatory requirements and Good Manufacturing Practice requirements.

Each label will carry the following information:

- The name, postal address + telephone no. of the manufacturer (i.e., the sponsor);
- The product reference codes;
- The bar code enabling product traceability;
- The list of the medical device components;
- The batch no.;
- The end of use date;
- The special storage conditions;
- The word “sterile”;
- The warnings and precautions to be taken.

The following details will be added to the original label but will not obscure the wording already printed on the initial packaging:

- Name of the coordinating investigator;
- Postal address and telephone number of the coordinating investigator;
- The ID RCB number;
- The wording “For biomedical research only”;
- a free text field entry to enter the patient identification number.

The B-DYN devices are previously labelled by the sponsor. These are listed in a follow-up file (follow-up application in QUANTA VIEW®) allowing monitoring of the devices implanted in patients, the devices available in each centre and the real time supply of the centres.

The medical devices will be stored in a place dedicated for this purpose or in the hospital pharmacy.

The medical devices for this study may not be used for an alternative use other than that defined in the protocol. The investigator or centre staff are not, under any circumstances, authorised to provide the products to another investigator or another centre or use them for an alternative purpose.

6.8. MEASURES TO ENSURE IMPARTIALITY OF JUDGEMENT

The methods used to guarantee blinding with regard to the primary end point are described in section **Erreur ! Source du renvoi introuvable.**. The methods used to guarantee impartiality of judgement concerning deviations are listed in the blind data review (cf. section **Erreur ! Source du renvoi introuvable.**).

7. SELECTION AND EXCLUSION OF THE PARTICIPANTS FOR THE RESEARCH

7.1. INCLUSION CRITERIA

Disease related criteria:

1. Stenosis on 1 or 2 adjacent segments (grade C or D according to Schizas classification) on MRI
2. Spondylolisthesis grade 1 or no spondylolisthesis
3. Pseudoclaudication (Pseudoclamping) on one or both legs and back pain (VAS score> 30)
4. Patient who has failed well-managed medical treatment that has not resulted in long-lasting symptom relief (duration of symptoms > 6 months);
5. Patient with no contraindication to fusion or the application of B-Dyn®.

Population-related criteria

1. Subject: both sexes, 40 years of age and older
2. Patient who has given free, informed and written consent to participate in the study;
3. Patient who is able to respond to questionnaires and who can communicate in the language of the study country ;
   Patient affiliated to a social security scheme or entitled to a social security scheme.

7.2. NON INCLUSION CRITERIA

Disease related criteria:

1. Spondylolisthesis of grade > 1
2. Degenerative Scoliosis (Cobb angle > 20°);
3. History of fusion for spinal stenosis or vertebral instability
4. Stenosis not caused by from degenerative changes.
5. Isolated disc herniation
6. Other specific vertebral damage (for example: ankylosing spondylitis, cancer or neurological disorders)
7. History of vertebral fractures resulting from the compression at the instrumented level
8. History of osteoporotic fractures
9. Psychological disorders (e.g. dementia or substance abuse) that lead to an inability to participate in the study
10. Intervention required on more than 3 vertebral levels;
11. Chronic infection

Population related criteria:

1. Withdrawal of consent;
2. Pregnancy;
3. Breastfeeding woman;
4. Participation in a clinical trial in the 3 months prior to the initial visit;
5. Drug addiction;
6. Predicted unavailability during study. Patient deprived of liberty or under guardianship.

Medical Device related criteria:

1. Allergy to any of the components of the medical device.

7.3. PROCEDURE OF PREMATURE DISCONTINUATION OF USE OF THE MEDICAL DEVICE

There is no procedure for early discontinuation of use per se. The decision to explant or replace the device is a decision made by the surgeon as a result of a complication or malfunction. The surgeon may take the decision as to the opportunity to use this measure, the methods used and follow-up to be instituted.

8. TREATMENT USED ON THE INDIVIDUALS WHO WILL PARTICIPATE IN THE RESEARCH OTHER THAN THE MEDICAL DEVICE TO WHICH THE RESEARCH IS RELATED

8.1. DESCRIPTION OF THE MEDICAL DEVICE USED FOR RESEARCH PURPOSES INCLUDING THE IMPLEMENTATION OF THE MEDICAL DEVICE TO WHICH THE RESEARCH RELATE, AS WELL AS THE MONITORING PERIOD

8.1.1. DEVICE UNDER STUDY :

The B-Dyn ® device is described in the paragraph 4.1

You can also refer to appendices 20.3 and 20.4

8.1.2. COMPARATOR : FUSION

The bolted fusion, with or without cage is described in the paragraph 6.4.2

8.2. AUTHORIZED AND PROHIBITED MEDICINES AND TREATMENTS, UNDER THE PROTOCOL, INCLUDING EMERGENCY MEDICINES NON APPLICABLE.

NOT APPLICABLE

9. PERFORMANCE ASSESSMENT

9.1. DESCRIPTION OF EFFICACY ASSESSMENT PARAMETERS

9.1.1. PRIMARY END POINT

The main criterion is the degree of functional disability related to low back pain. It will be measured using the Oswestry Disability Index (ODI) at the 12th month compared to the baseline data.

9.1.2. SECONDARY ENDPOINTS

1. the mobility of the instrumented level and adjacent levels will be measured at inclusion, 2 months, 12 months and 60 months post intervention using dynamic X-rays of the lumbar spine: the degree of mobility is calculated by subtracting the angle that is formed in flexure by the tangent of the upper layer of the upper vertebra, and the tangent of the lower layer to the angle formed by these extending tangents. For double instrumentations, an average of the mobility of the two mobile levels is pulled off.

2. the degree of functional disability related to lumbar and radicular pain will be measured by the Oswestry Disability Index (ODI) at inclusion, 2 months, 12 months and 60 months post-intervention;

3. the intensity of radicular and lumbar pain will be assessed by the VAS scale (0-100) at inclusion, 2 months, 12 months and 60 months post-intervention

4. the quality of life will be assessed by the SF-12 score at inclusion, 2 months, 12 months and 60 months post-intervention;

5. anxiety will be measured using the Hospital Anxiety and Depression Scale (HAD) at inclusion, 2 months, 12 months and 60 months post intervention;

6. radiological parameters such as lumbar lordosis (LL), instrumented level segmental lordosis, disk height of the disk above the instrumentation, and pelvic parameters (pelvic incidence PI, Sacral slope (Ps) and pelvic tilt (PT) will be measured at inclusion, 2 months, 12 months and 60 months post intervention using whole body imaging (tele-rachis/ Tele-spine or EOS)

7. Neurological and motion status will be assessed at the instrumented level and adjacent levels (right and left), by measuring motor skills, feeling of touch and stinging sensation at inclusion, 2 months, 12 months and 60 months post-intervention. Various tools will be used: MRC scale (which evaluates motor function from 0: no movement/contractions to 5: normal muscle strength); another scale will be used: from 0 (Absent) to 2 (Normal) to evaluate the feeling of touch and sting.

8. The walking distance will be evaluated by self-paced test at inclusion, 2 months, 12 months and 60 months post-intervention (patient will walk maximum possible distance)

9. The rate of re-intervention on the instrumented level or adjacent level during the study (up to 60 months). A re-operation during the study is defined as a secondary intervention at the instrumented level or adjacent level for any reason (infectious or mechanical): revision, implant removal (explantation), fusion, and need for additional fixation. etc

10. If a patient has one (or more) of the following conditions, he/she is considered to have an adjacent syndrome during the follow-up until the 60th month,

- **Adjacent radiological syndrome**: observed from simple and dynamic radiology and from MRI. It is defined by a narrowing of > 3 mm of the disk height, a posterior opening > 5° and sliding progression > 3 mm compared to the pre-operative data of the lateral bending radiology. On the MRI, it is defined by the postoperative progression of disc degeneration according to the Pfirrmann classification, as well as the progression of spinal canal stenosis evaluated according to the classification of Imagama et al [21]. The 1 grade progression of disk degeneration or spinal canal stenosis on MRI is considered an adjacent radiological syndrome.
- **Adjacent symptomatic syndrome**: is diagnosed when clinical symptoms such as radicular pain or intermittent claudications deteriorate after surgery, and that the lesion responsible for the symptoms is the one adjacent to the fused level (on MRI).
- **Surgical Adjacent Syndrome**: is defined as an adjacent symptomatic syndrome, for which surgery is required to treat neurological deterioration at the adjacent degenerative segment.

9.2. METHODS AND TIMELINE FOR MEASURING, COLLECTING AND ANALYSING THE PARAMETERS FOR ASSESSING EFFECTIVENESS

The data collection calendar to assess effectiveness is provided in the general outline (cf. the general outline in paragraph 6.2.1).

The various measurement tools and questionnaires used in this trial are listed below:

9.2.1. ODI (OSWESTRY DISABILITY INDEX)

The Oswestry questionnaire helps assess the symptoms and severity of back pain, as well as the impairment on daily life activities. The questionnaire contains 10 questions, concerning: pain, personal care, loads, walking ability, sitting position, standing position, sleep, sexual life, social life, travels. Each question offers 6 answers, with a score of 0 to 6 that the patient must choose; score 0 corresponds to a normal function, and score 6 to a very diminished function. (CF appendix 20.3).

The score obtained is multiplied by 2 to get a percentage of disability, with 0% for the absence of disability, and 100% for the most important disability. Completion of the test takes about 5 minutes

The Oswestry Disability Index will be measured at inclusion, 2nd month, 12th month and 60th month post-surgery.

9.2.2. VAS SCALE TO ASSESS THE PAIN INTENSITY

The visual analogue scale is shaped as a graduated ruler: from 0 to 100; 0 means that the subject has no pain and 100 is the maximum pain he can bear. It's a self-assessment scale. It is sensitive, reproducible, reliable and validated in both acute and chronic pain situations.

The intensity of the lumbar and radicular pain will be measured at inclusion on the first post-operative day, at the 2nd month, 12th month and 60th month post-surgery.

9.2.3. QUESTIONNAIRE ON THE QUALITY OF LIFE SF12

The SF-12 test is an abridged version of the « Medical Outcomes Study Short-Form General Health Survey »(SF-36) with only 12 of the 36 questions. The SF 12 generates two scores: a mental and social quality of life score and a physical quality of life score. The quality of life will be measured at inclusion, at the 2nd month, at the 12th month and at the 60th month post-surgery. (See Appendix 20.7).

9.2.4. THE HOSPITAL ANXIETY AND DEPRESSION SCALE. (HAD)

The HAD scale is a tool that detects anxiety and depressive disorders. It comprises 14 items rated from 0 to 3. There are seven questions related to anxiety (total A) and seven others related to the depressive dimension (total D); this provides two scores (maximum score of each score = 21). (cf. appendix 20.9)

The depression and anxiety score will be measured at inclusion on the first post-operative day, at the 2nd month, the 12th month, and the 60th month post-surgery.

9.2.5. NEUROLOGICAL AND MOTOR STATUS ASSESSMENT

Different tools will be used: an MRC scale (which evaluates the motor function: 0 means no movement/contractions, 5 means normal muscle strength), and another scale: 0 means Absent and 2 means Normal ; this is used to assess the sensation of touch and sting. The neurological and motor status will be assessed at the L4, L5 and S1 levels (right and left) (See Appendix 20.8)

9.2.6. SIMPLE RADIOGRAPHY (TELE RACHIS OR EOS)

This is a face and profil X-ray, on which the sagittal alignment parameters will be measured. It will be carried out at the 2nd month, the 12th month, and the 60th month post intervention.

An independent radiologist will be in charge of the centralized reading.

9.2.7. DYNAMIC RADIOGRAPHY

This is an radiograph, on which the mobility of the instrumented level and the adjacent levels will be measured.

During this radiograph, the patient will be asked to bend down until he/she reaches the painful threshold in flexion and extension, and in lateral inclination. This image should focus on the instrumented level.

It will be carried out at the 2nd month, the 12th month, and the 60th month post intervention.

An independent radiologist will be in charge of the centralized reading.

9.2.8. MRI

This is an examination to confirm a stenosis and an adjacent syndrome. It will be performed at the 12th month , and the 60th month.

10. SAFETY ASSESSMENT

10.1. DESCRIPTION OF SAFETY ASSESSMENT PARAMETERS

The criteria for assessing safety and tolerance shall be:

- The number of patients who experienced at least one adverse event during the follow-up period.
- The number of patients who experienced a serious adverse event during the follow-up period,
- The short term and long-term, pre-operative and post-operative complications rate

10.2. INTENDED METHODS AND SCHEDULE TO MEASURE, RECORD AND ANALYSE SAFETY ASSESSMENT PARAMETERS

The schedule for data collection enabling assessment of safety is shown in study design section (Cf. Plan of the study in section **Erreur ! Source du renvoi introuvable.**.).

10.3. PROCEDURES IN PLACE FOR R FOR ADVERSE EVENT RECORDING AND REPORTING

10.3.1. DEFINITION OF ADVERSE EVENTS (AE)/ADVERSE DEVICE EVENTS (ADE)

Adverse event (AE): any untoward or unfavorable medical occurrence in a human beings undergoing research involving human subject, whether or not considered related to the subject's participation in the research.

Adverse device effect (ADE): any untoward and unintended responses to the use of an investigational medical device. This includes any adverse event resulting from insufficiencies or inadequacies in the instructions for use, the deployment, the implantation, the installation, the operation, or any malfunction of the investigational medical device - This includes any event that is a result of a use error or intentional misuse.

Each AE must be classified by the investigator as serious or non-serious. This classification determines the procedure to be followed in reporting the event to the Sponsor Cousin Biotech.

This definition includes events related to both the investigational device and the comparator. It also includes events relating to implantation of the device.

The investigator must record all AEs observed directly and all AEs reported by the patient using suitable medical terminology. During visits, patient will be questioned by the investigator about the onset of any AEs throughout the entire study.

Adverse events are recorded in the case report form. The investigator must indicate any possible relationship between the investigational device and the adverse event, as well as the relationship between implantation of the device and the adverse event.

The safety evaluation criteria must be evaluated and recorded by the investigators throughout the study, and collected by the Sponsor during monitoring visits. These comprise symptoms, dates, outcome, measures taken, and, where necessary, the results of any examinations and laboratory tests.

The investigator must record in the "adverse events" section of the case report form any events significant for the study:

1. Reported by the patient (spontaneously or during the questioning) or observed by the investigator (during clinical examination);
2. Whether or not they are considered attributable to the device or to the surgery process;
3. the record of the event will comprise the following information:

- Type of event (brief description in objective rather than interpretive terms);
- Date of onset and date of resolution of the adverse event (where applicable);
- Seriousness of the event (i.e. serious or not serious);
- Outcome of the event (resolution with or without sequelae);
- Measures taken regarding the implant (removal, replacement, adjustment);
- Causal relationship with the investigational device (unlikely, possible, probable, certain);
- Causal relationship with implantation of the device (unlikely, possible, probable, certain).

Patients may contact the investigator about any adverse events occurring during the study or after the end of the study.

Defects in the device in terms of its identity, quality, durability, reliability, safety or its performances must be recorded throughout the entire duration of the study. Such deficiencies will be reported at least as adverse events.

10.3.2. DEFINITION OF SERIOUS ADVERSE EVENTS (SAE)

Any adverse event which:

1. Results in death (including deaths due to progression of the disease being treated);
2. Places the life of the person involved in the research in danger (i.e., immediately life-threatening at the time of the adverse event independently of the consequences of corrective or palliative treatment);
3. Requires hospitalisation or prolongs hospitalisation;
4. Causes incapacity (any clinically significant, temporary or permanent handicap) or severe or sustainable handicap;
5. Results in a congenital abnormality or malformation.

Planned hospitalisation for a pre-existing disorder or a procedure required by the protocol without serious deterioration in health is not deemed to be a serious adverse event.

Other events which do not meet the criteria listed above may be deemed to be "potentially serious". These events may be declared in the same way as per the declaration of serious adverse events on the medical judgement of the investigator or COUSIN BIOTECH.

10.3.3. EXPECTED/UNEXPECTED NATURE OF SERIOUS ADVERSE EVENTS

10.3.3.1. *EXPECTED ADVERSE EVENTS DUE TO THE DEVICE OR PROCEDURE*

The expected complications are as follows:

1. All of the possible adverse events associated with spinal surgery and without instrumentation are possible:
    - Infection
    - Pseudomeningocele, fistula, breach dura, persistent CSF leakage, meningitis
    - Loss of neurological function, sensorial and/or motor, including complete or incomplete paralysis, dysesthesias, hyperesthesia, anesthesia, paresthesia, appearance of radiculopathy, and/or the development or continuation of pain, numbness, neuroma, spasms, sensory loss, tingling sensation, and/or visual deficits
    - Cauda equina syndrome, neuropathy, transient or permanent neurological deficits, paraplegia, paraparesis, reflex deficits, irritation, arachnoïditis, and/or muscle loss
    - Urinary retention or loss of bladder control or other types of urological system compromise
    - Scar formation possibly causing by a neurological compromise or compression around nerves and/or pain
    - Fracture, microfracture, resorption, damage or penetration of any spinal bone (including the sacrum, pedicles, and/or vertebral body) and/or bone graft or bone graft harvest site at,

above and/or below the level of surgery

- Herniated nucleus pulposus, disc disruption or degeneration at, above, or below the level of surgery, canal adjacent stenosis
- Non-union or pseudarthrosis, delayed union. Mal union
- Cessation of any potential growth of the operated portion of the spine
- Loss of or increase in spinal mobility or function
- Inability to perform the activities of daily living
- Bone loss or decrease in bone density
- Graft donor site complications including pain, fracture, or wound healing problems
- Ileus, gastritis, bowel obstruction or loss of bowel control or other types of gastrointestinal system compromise
- Hemorrhage, hematoma, occlusion, seroma, edema, hypertension, embolism, stroke, excessive bleeding, phlebitis, wound necrosis, wound dehiscence, damage to blood vessels, or other types of cardiovascular system compromise
- Reproduction system compromise, sterility, sexual dysfunction
- Development of respiratory problems, e.g. pulmonary embolism, atelectasis, bronchitis, pneumonia, etc
- Change in mental status
- Death

2. All of the possible adverse events associated with spinal surgery with instrumentation are possible. A listing of potential adverse events linked to the medical device includes, not limited to:
    - Early or late loosening of any or all of the components
    - Disassembly, bending and/or breakage of any or all of the components (screw breakage)
    - Foreign body (allergic) reaction to implants, debris, corrosion products (from crevice, fretting, and/or general corrosion), including metallosis, tumor formation and/or autoimmune disease
    - Pressure on the skin from components parts with inadequate tissue coverage over the implant possibly causing skin penetration, irritation, fibrosis, neurosis, and/or pain
    - Tissue or nerve damage caused by improper positioning and placement of implants or instruments
    - Post-operative change in spinal curvature, loss of correction, height, and/or reduction

10.3.3.2. *UNEXPECTED SERIOUS ADVERSE DEVICE EFFECTS (USADE)*

A serious adverse effect, the type, severity, outcome or complications of which are inconsistent with known information or information appearing in the instructions for use leaflet (Cf. annexe **Erreur ! Source du renvoi introuvable.**) when it carries the CE mark and in the protocol or investigator's brochure when it does not carry the CE mark.

10.3.4. ASSESSMENT OF THE SEVERITY OF AN ADVERSE EVENT AND RELATIONSHIP WITH THE IMPLANTED DEVICE

The investigator will assess the severity of the adverse event as follows in the case report form:

MILD	Not restricting everyday activities
MODERATE	Resulting in partial restriction of everyday activities
INTENSITY	Causing an inability to carry out everyday activities

The **seriousness** and **intensity** of an adverse event must be distinguished. **Severity** is a measurement of intensity and a **severe** reaction is therefore not necessarily a **serious** reaction. The investigator must also assess the causal

relationship between the adverse event and the implantation of the device based on the information available and using the following criteria:

UNRELATED	There is no chronological relationship between implantation of the device and the event. Thus, either the cause of the event has been identified or the investigational device cannot be implicated.
RELATIONSHIP UNLIKELY	The time to onset of the event is relatively inconsistent with the implantation of the device; other possible causes exist.
RELATIONSHIP POSSIBLE	A chronological relationship exists, but other causes appear more likely; however, the implantation of the device cannot be ruled out.
RELATIONSHIP PROBABLE	A chronological relationship exists, and while other causes are possible, they are unlikely.

10.3.5. DURATION OF THE PERIOD OF NOTIFICATION OF SAE TO THE SPONSOR

The collection period for AEs and SAEs will begin as soon as informed consent has been signed and end at the 24 month visit.

This period, however, may be extended if the investigator considers that it is necessary to follow-up the event for a longer period of time or for an unresolved SAEs.

All adverse events, whether or not related to the implanted device, must be followed-up until they have resolved or until the investigator considers them to be chronic or stable or until the patients' participation in the study has ended (i.e., a final report has been produced for this patient). In addition, all serious and non-serious adverse events which are deemed by the investigator to be potentially related to the study device or to the procedure used for the device must be followed-up, even after the end of the study.

The instructions to report changes in ongoing adverse events during the patient's participation in the study are shown in the corresponding pages of the case report form.

All events which occur in patients during this period must be reported to COUSIN BIOTECH by the investigator as soon as he/she becomes aware of them and whether or not they are deemed to be related to the device.

Any event which occurs after the end of the study and which the investigator assesses as being potentially related to the research must also be reported as an adverse event.

10.3.6. NOTIFICATION BY THE INVESTIGATOR TO THE SPONSOR

The investigator must notify to the sponsor:

Any SAEs, whether or not related to the medical device or procedure used, and whether expected or unexpected in nature, without delay from the day on which he/she becomes aware of it.

Serious adverse events will be recorded in the "Adverse event" section of the eCRF. The investigator will complete and approve the SAE notification form in the eCRF.

He/she will, wherever possible, submit all documents which may be of use to the sponsor (all hospitalisation reports/letters/anonymised investigation results explaining the circumstances of the SAE, its treatment and its outcome. Notifications will be made automatically via the eCRF to the COUSIN BIOTECH Head of Regulatory Affairs:

Franck Pelletier

E-mail: f.pelletier@cousin-biotech.com

If information is missing from the initial notification form this must be followed by a "follow-on" notification (using a new SAE notification form) within five calendar days following the discovery of the SAE.

If necessary, the investigator can notify an SAE using a paper form.

On receipt of the SAEs form, it will be examined by a senior member of the sponsor's device's vigilance who will:

1. Assess whether the SAE was expected or unexpected;
2. Assess the causal relationship between the SAE and the medical device or implantation of the device;
3. Contact the Study Coordinator, the notifying department, to obtain information about the circumstances of onset of the SAE and about the treatment and outcome of the event.

Any SAE for which a relationship with the investigational medicinal device has not been completely excluded will be declared to ANSM by the sponsor.

The incidence of expected SAEs will be monitored by the sponsor's SAEs committee. If the incidence of an expected SAEs increases this will be redefined as unexpected and a new declaration will be made to ANSM.

NOTE: If the investigator is not immediately aware of an SAEs, he/she must report this within 24 hours of becoming aware of it, explaining how he/she became aware of it.

10.3.7. DECLARATION BY THE SPONSOR TO THE HEALTH AUTHORITIES

For any events occurring during this research and liable to be related to the medical device and for any SAE related to the procedure used for the device, after becoming aware of this SAE the sponsor will make a declaration by e-mail to ANSM at: EC.DM-COS@ansm.sante.fr

1. Without delay for SAE which resulted in death, was life-threatening or associated with an imminent risk of death or for a serious injury or disease which justified prompt curative treatment or any new information relating to this;
2. Immediately and within 7 days for the other SAE

If an initial declaration of an SAE is incomplete, as soon as the further information has been received the sponsor will submit a reference numbered follow-on report for this SAE to ANSM.

Annually following the anniversary date of the inclusion of the first patient into the study and throughout the duration of the study, on request the sponsor will submit to ANSM and to the EC a safety report taking account of all available safety information. This report will include, among other things, a list of all suspected serious adverse events and an analysis of safety information concerning people taking part in the research.

If no expected or unexpected SAE is declared in this study, only an annual electronic e-mail will be sent to ANSM and to the EC to inform them that no SAE has occurred. The development and declaration of expected and unexpected SAE will be checked routinely in the monitoring visits.

A summary of the final report will be submitted to ANSM and to the EC within a period of one year following the end of the research.

10.4. EMERGING SAFETY ISSUE

10.4.1. DEFINITION OF EMERGING SAFETY ISSUE

This refers to any new information which may result in:

1. A reassessment of the benefit/risk balance of the research or on the medical device on which the research is being carried out;
2. Changes :
   - To the use of the medical device;
   - To the conduct of the research;
   - To documents relating to the research.
3. Suspension, interruption or a change to the research protocol.

10.4.2. DECLARATION BY THE SPONSOR TO THE HEALTH COMPETENT AUTHORITIES

The Sponsor must inform competent Authorities of any emerging safety issue and, where applicable, any measures taken. An emerging safety issue may also correspond to an unexpected serious adverse device effect or an SAE potentially associated with implantation of the MD. In this case, a double declaration must be made of the event in question. Follow-up procedure and duration for patients after onset of an adverse event

10.5. FOLLOW-UP PROCEDURE AND DURATION FOR PATIENTS AFTER ONSET OF AN ADVERSE EVENT

Any person presenting an adverse effect/event (whether serious or not) will receive follow-up appropriate to their condition and will be monitored until the event has resolved or until the end of the research. If necessary, use of the medical device may be suspended. who develops an adverse effect/event (serious or non-serious) will receive appropriate management for his/her condition and be followed-up until the event has resolved or until the end of the research. If necessary, the use of the medical device may be interrupted.

10.6. MEASURES TO BE TAKEN TO ENSURE SAFETY IN THE CASE OF DEVICE DEFICIENCY, INCLUDING ISOLATED MALFUNCTION OF THE DEVICE WITH NO CLINICAL REPERCUSSIONS AND MISUSE

10.6.1. DEFINITION OF FAILURE OF A MEDICAL DEVICE

Inadequacy of the investigational medical device relating to its identity, quality, lifespan, reliability, safety or performance. Defects include malfunctions, usage errors or inadequate information provided by the manufacturer.

10.6.2. DECLARATION BY THE SPONSOR TO THE HEALTH COMPETENT AUTHORITIES

After becoming aware of the failure the sponsor will submit an immediate declaration after 7 days by e-mail to ANSM at: EC.DM-COS@ansm.sante.fr, pour

1. Any failure of the investigational medical device which may have resulted in a serious adverse event if:

a) Appropriate action was not taken or;

b) A procedure was not conducted or;

c) If the circumstances had been less “random”.

11. STATISTICAL ANALYSES

11.1. NUMBER OF SUBJECTS REQUIRED

The objective of the project is to look for a non-inferiority of the «B-DYN» group compared to the «bolted fusion with or without cage» group, on the degree of functional disability after surgery evaluated by the Oswestry disability index (ODI) at the 12th month post-surgery.

According to the literature, patients with a fusion shows 37.1% ODI decrease by 1-year, compared to the baseline.

Considering this hypothesis, a sample size of N= 188 patients (94 “Bdyn” / 94 “Fusion”) will be a 90% demonstration proof of a non-inferiority by considering a non-inferiority margin of -2 and a standard deviation of 6.7. Considering a 15% attrition rate, we will include a total of 216 patients. An intermediate analysis is planned once 100 patients will have reached the main assessment criterion.

11.2. DESCRIPTION OF THE STATISTICAL METHODS

This is a randomized, single-blind, comparative study.

All analyses will be described and detailed in the statistical analysis plan, and will be drawn up by the statistician in charge of the study, and validated before the database is frozen.

The analysis plan will be reviewed by the statistical and clinical team, when the data are complete and available, and before the unblinding at the Blind review meeting. During the review, decisions will be made on the appropriate course of action to be taken, in relation to contentious cases (including false data), this will also be detailed in the final statistical analysis plan. This document will be placed in the test file prior to the unblinding.

11.2.1. STATISTICAL METHODS / STATISTICAL ANALYSES PLAN

All analyses will be performed with the SAS® version 9.4 or the later version.

All analyses will be described and detailed in the statistical analysis plan. This document will be blindly written and validated before the Blind review. Any changes made to this document after the Blind review will be subject to an amendment to the statistical analysis plan. The last validated version of the Statistical Analysis Plan prior to unblinding will be considered as the final version of this document.

11.2.2. DESCRIPTION OF THE POPULATION

Demographic and initial characteristics will be described for both treatment groups.

The previous and concomitant treatments will be coded by ATC, code from the WHODRUG medical dictionary.

The medical history and the associated pathology will be coded by the MEdDRA® medical dictionary.

11.2.3. FINAL STATISTICAL ANALYSES

11.2.3.1. *DESCRIPTION OF THE SUBJECTS FOR THE STUDY, AND VERIFICATION OF THE COMPARABILIITY AT INCLUSION*

A comparative analysis will be carried out on the patient population, which can be evaluated for tolerance, for all the documented characteristics: initial data and evaluation criteria.

For the quantitative criteria, the initial and final values, and the variation will be described by average, by standard deviation or by median (quartiles), depending on the distribution (normal or not) of the data, with minimum and maximum, and with 95% CI if applicable. For qualitative criteria: percentages and 95% CI will be calculated.

The characteristics of inclusion will be described for each group. As the study is randomized, no statistical tests will be used to compare patient's characteristics at inclusion.

11.2.3.2. *ANALYSIS OF THE MAIN CRITERION*

Each time 100 patients meet the main criteria of evaluation, the analysis will be conducted with intent to treat each of them. This analysis will use a triangular test.

The analysis of the main judgement criterion will consist of comparing the Oswestry Disability Index (ODI) between the "B-DYN" group and the "Bolted Fusion with or without cage" group at M12, adjusted to the base score value by a covariance analysis (ANCOVA). A random effect at the center level will be introduced.

11.2.3.3. *ANALYSIS OF SECONDARY CRITERIA OF EFFICIENCY*

Analysis of the B-DYN effect on the evolution of the Oswestry disability index, the lumbar and radicular pain VAS score, the quality of life score, anxiety, and the range of radiological parameters (mobility, etc.), between the inclusion, M2 and M12, and M60. The motor and neurological status scores will also be assessed in a mixed ANCOVA model for repeated measurements.

In case of a non-compliance with the validity conditions of the test, a transformation of variables can be applied. If this method shows to be insufficient, a rank analysis will be implemented. A random effect at the center level will be introduced into the model. For all these tests, the bilateral significance threshold is set at 5%. The comparison of the relapse rate and surgical re-operations (explantations, revisions and re-operations whatever the cause) between the two groups will be done using a Chi2 or Fisher test in case of insufficient numbers.

11.2.3.4. *ANALYSIS OF THE CLINICAL TOLERANCE*

The occurrence of these events (revision, explantation) will be described by using the Kaplan-Meier method, and it will be compared between the two groups by the log-rank test.

The incidence rates of adverse events will be calculated and compared between the groups using Chi² or Fisher in case of insufficient numbers.

The intensity of adverse events will be compared between the groups using Chi² or Fisher in case of insufficient numbers.

The incidence of Aes will be tabulated by preferred system and/or organ, and by the term defined by the MedDra classification.

A particular attention will be paid to patients who have had at least one severe adverse event with severe intensity, causing the explantation of the tested device; or if the severe adverse event is judged in relation to the treatment being tested (possible, severe or certain).

The analysis of adverse events will be conducted through a "patient" approach rather than an "event" approach.

For all these tests, the bilateral significance threshold is set at 5%.

11.3. DEGREE OF STATISTICAL SIGNIFICANCE

Cf. the paragraph 11.2.3

11.4. METHODS OF ACCOUNTING FOR MISSING, UNUSED OR INVALID DATA

Data quality control is programmed to detect missing and inconsistent data. All missing data will be searched in the source folder. If the missing data cannot be retrieved by the CRA (Clinical Research Associate) of the study, a multiple imputation procedure may be considered based on the number of missing data and the underlying mechanism.

11.5. MANAGING CHANGES ON THE ANALYSES PLAN

The statistical analysis plan will be written blind with respect to the data. If changes must be done to the methods described in the « Statistical Analysis » paragraph of this protocol, they will be validated by the referent statistician in the Statistical Analysis Plan.

11.6. SELECTION OF INDIVIDUALS TO BE INCLUDED IN THE ANALYSES

11.6.1. INTENT TO TREAT POPULATION (ITT)

All randomized patients who received any of the interventions. This population coincides with the population of patients assessed for tolerance.

All the patients that have given consent, and have been randomized will be analyzed according to their group of randomization.

For tolerance analyses, in case of randomization errors (device set up), patients will be analyzed according to the procedure they have received.

11.6.2. PER PROTOCOLE (PP)

All patients who completed the study without any major deviation from the protocol.
To be assessable, the patient:

1. Must meet all inclusion criteria, and not meet any of the non-inclusion criteria;
2. Must have been through the procedure selected from randomization;
3. Must not show any sign of post-randomization deviations that is considered as « major »:
    - Going through prohibited treatments;
    - Failure to meet protocol deadlines for visits;
    - Absence of conscent ;
    - Repeated non-compliance with protocol requirements.
4. Must be assessable for the primary criterion.

All deviations will be reviewed and classified as major/minor at a Blind Review meeting.
Efficiency analyses will be conducted in ITT and PP.

12. ACCESS RIGHTS TO THE SOURCE DOCUMENTS AND DATA

12.1. Rights of access to data

People who have direct access, pursuant to current legislative and regulatory requirements and particularly articles L.1121-3 and R.5121-13 of the French Code of Public Health (*e.g.*, investigators, staff responsible for quality control, monitors, clinical research associates, auditors and all staff requested to work in studies) will take all of the necessary precautions in order to ensure the confidentiality of the information relating to the investigational medicinal products, studies and people taking part in them, particularly with respect to their identity and the results obtained. The data collected by these people during quality control or audits are therefore anonymised.

12.2. DESCRIPTION OF VARIABLES COLLECTED

Data from the study will be collected directly from the e-CRF as the visits go by. These data will be validated by the investigator who will sign (manually or electronically) the observation notebooks.

Here below are the collected information for this study:

- Demographic data ;
- Background information ;
- Concomitant pathologies and associated treatments;
- History of the disease;
- Clinical examination;
- Radiographic examination;
- Surgical intervention ;
- Post surgical follow-up :
  - Clinical test ;
  - Adverse events.

The further questionnaires will also be used:

12.2.1. OSWERSTY QUESTIONNAIRE

It helps assess the symptoms and the intensity of the lower back pain, and how it affects the patient's daily life activities.

12.2.2. SF 12 QUALITY OF LIFE QUESTIONNAIRE

The SF 12 provides two scores: a score on the mental and social quality of life and a score on the physical quality of life.

12.2.3. ASSESSMENT OF THE NEUROLOGICAL AND MOTOR STATUS

To assess the neurological and motor status.

12.2.4. VISUAL ANALOGICAL SCALE

The CRF will include a visual analogical scale of the lumbar and radicular pain (VAS).

12.2.5. THE HOSPITAL ANXIETY AND DEPRESSION SCALE

To assess the degree of anxiety and depression.

12.3. IDENTIFICATION OF SOURCE DATA

The investigator undertakes to provide direct access to the original data to COUSIN BIOTECH or to any person delegated to represent the company, and to the regulatory authorities.
Original documents will consist of all of the information and results of investigations shown in the medical file of people taking part in the research.
The minimum data set which will appear in the original file of patients included in the study are:

- Participation in the study,
- Date of information and inclusion of the patient into the study (signature of consent)
- Date of visits,
- Past medical and surgical history,
- The procedure allocated to the patient,
- concomitant treatments,
- Development of adverse events,
- Development of serious adverse events.

These data must enable the different assessments made in the CRF to be “reconstructed”.

13. QUALITY CONTROL AND INSURANCE

The research data will be collected using the QUANTA VIEW The Clinical eBox [1] Electronic Case Report Form.
The data will be collected in real time by the clinicians and processed in accordance with current legislation.
Monitoring will be provided by the clinical research associates in each investigating centre throughout the duration of the study in order to ensure that the study is conducted correctly.
Signature and compliance of each patient's consent will be routinely checked. The original documents will be reviewed to ensure that the data are consistent with the case report form. Monitoring will be conducted in accordance with ICH E6 recommendations.
The investigator and staff involved in the study must be available during the monitoring visits and any audits or inspections and provide sufficient time for these to be conducted.
Quality control will be carried out by the Clinical Research Associate. As the sponsor has classified this study as *increased* monitoring status which means that the CRA will carry out 1 set up visit, the number of monitoring visits required to check 20% of the case report forms and a closure visit in each centre. All of the case report form data and the presence of all signed consents will be checked. The presence of all signed consents will be checked. These visits will be carried out according to the QM standard operating procedures. A visit report will be drawn up following these visits and sent within a maximum period of 7 days to the project lead who will approve these.
The data submitted will be checked and subject to data management in accordance with QUANTA MEDICAL requirements and procedures and consistent with professional requirements.
An audit may also be carried out by COUSIN BIOTECH or any organisation appointed by the sponsor or by the Health Authorities.

13.1. RISK MINIMISATION PLAN

The risk minimization plan which was implemented describes and qualifies (in terms of likelihood and severity) the risks associated with the study. These risks are classified as follows:

- Risks relating to participants' rights;
- Risks relating to participants' safety;
- Risks relating to the integrity of data and results.

Reduction actions are proposed for each risk identified.

13.2. QUALITY INSURANCE PLAN

The Quality Management Plan also called the Quality Assurance Plan (QAP), is suitable for the specific features of the study and type of risks it involves.
The QAP shows a list of the monitoring and control procedures which will be implemented in order to deal with non-compliances identified with targeted corrective actions.

1 QUANTA VIEW The Clinical eBox ™ is a registered trademark of QUANTA MEDICAL™

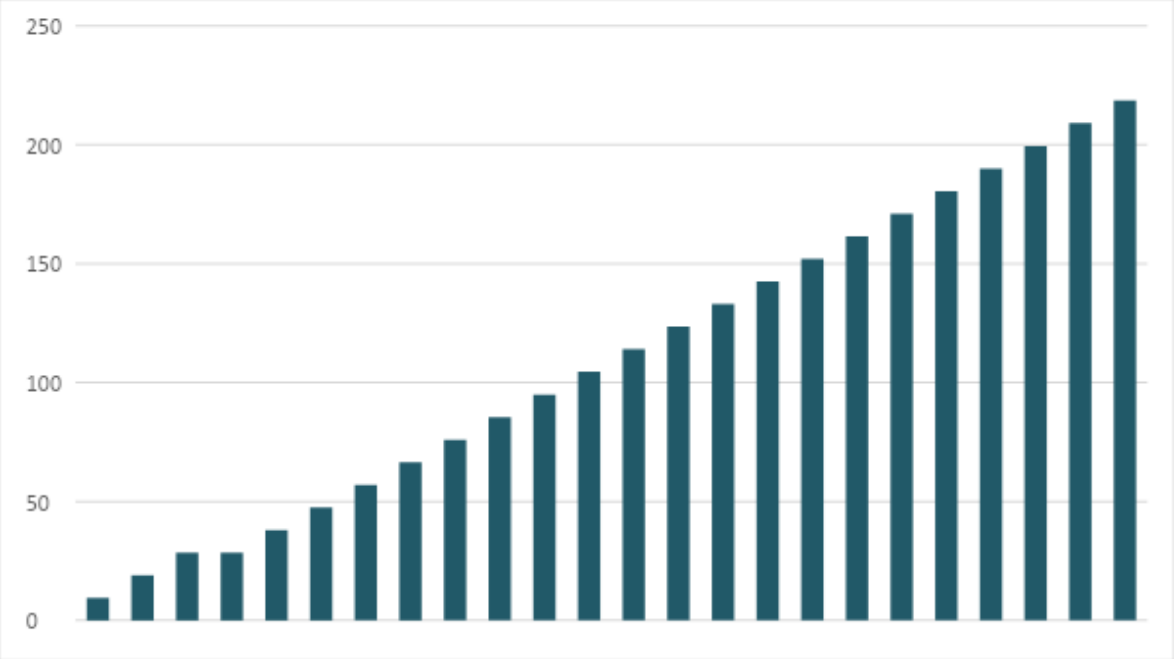
13.3. MONITORING AND INDICATORS

In accordance with in-house procedures, QM defines Quality and Performance indicators to be monitored and analysed during the study. The indicators will be proposed during the framework meeting and decided jointly.
An analysis of the indicators will be used to assess the quality of services provided for each project. The Performance and Quality indicators will be analysed monthly.

14. FEASIBILITY AND TIMELINE OF THE STUDY

The centers' recruitment is evaluated on the basis of the number of investigators per center, and on the basis of the recruitment potential per center: between 1 and 2 patients per month.

Inclusion curve



- Duration of study : 84 months
- Forecast of the inclusions start : May 2020
- End of inclusions date : May 2022
- End of follow up date : May 2027
- Analyses and results : November 2027

15. STUDY ORGANIZATION

15.1. STEERING COMMITTEE

It will consist of the clinical project initiators, the biostatistician in charge of the project, and the promoter's representatives.

It will define the general organisation, the conduct of the research, and it will coordinate the information flow. It will initially determine the methodology, and during the course of research, it will decide about the right conduct if an unanticipated event happens. It will also monitor the research process, especially, in terms of tolerance and adverse events.

The committee is made up of : the clinical project initiators (Pr Vincent POINTILLART and Dr Bertrand DEBONO) , the QM project manager (Rym BOULKEDID), the QM Project Director (Dr Othar ZOURABICHVILI), and of the promoter's representative as well as the Promoter's Material Supervisor.

For the sake of the cause, the following may be assisting members of this committee:

- One or more investigators;
- Placement instructor(s);
- A technician: IT manager or data-management-statistic or;
- A specialist invided on ad hoc basis

16. ETHICAL CONSIDERATIONS

16.1. DECLARATION STATING THAT THE RESEARCH WILL BE CONDUCTED IN ACCORDANCE WITH THE PROTOCOL, GOOD PRACTICE AND CURRENT LEGISLATIVE AND REGULATORY REQUIREMENTS

The sponsor and all investigators undertake to conduct this study in accordance with

- Law no. 2012-300 of 5 March 2012 on research involving human beings (the so-called Jardé law) modified by Order no. 2016-800 of 16 June 2016 and Decree no. 2016-1537 through which this law is applied;
- MEDDEV 2.7/3 revision 3 (May 2015) – Guidelines on the reporting of serious adverse events in clinical studies on medical devices:
- The Decision of 3 March 2017 setting out the form, content and methods for declaring adverse events and new findings in research, as described in section 1 of article L. 1121-1 of the French Code of Public Health (CSP) on an MD/IVDMD;
- The French Code of Public Health;
- The Declaration of Helsinki (latest version: October 2013);
- Good Clinical Practice (GCP);
- ICH (International Conference on Harmonization) recommendations and in particular ICH E6 (Good Clinical Practice);
- The law relating to data processing, files and freedoms (law n ° 78-17 amended in 2004)
- Deliberation no. 2018-153 of 3 May 2018 approving a reference methodology for the processing of personal data used in health research with recording of consent from the person concerned (MR-002) and rescinding deliberation no. 2016-262 of 21 July 2016;
- Law 2018-493 of 20 June 2018 on the protection of personal data;
- Standard NF EN ISO 14155 (May 2012) on clinical investigations on medical devices in human subjects.

They undertake to follow all legislative or regulatory requirements which may relate to the research.

16.2. PROTECTION OF PEOPLE

The protocol will be submitted for an opinion to the Ethics Committee (EC) and to ANSM for authorisation before inclusions begin.
Prior to inclusion in the study, each investigator must ensure that the patient is provided with all of the information about the study, in particular:

- The plan of the study: duration, visits, samples, etc.;
- The expected benefits and risks resulting from his/her participation;
- The EC opinion;
- The possibility of the patient to withdraw his/her consent at any time without giving his/her reasons.

The information will be provided using the information leaflet. This document must be initialled on each page by the patient and by the investigator at the inclusion visit V1.
Once the patient has given his/her accord the patient and investigator must sign and date the consent form.
A copy of the consent form will be given to the patient and another copy will be kept by the investigator.

16.3. INSURANCE

The study sponsor has taken out insurance with ……

16.4. AMENDMENT TO THE PROTOCOL

Any substantial amendment which affects the conduct of the study or patient safety, including changes to the objectives of the study, the plan of the study, the population, the study procedures or important administrative aspects must appear as an amendment to the protocol.
No substantial amendments to this protocol may be implemented without approval from the EC and/or authorisation from the Competent Authority.
In order to be submitted, any substantial modification must carry the signature of the co-ordinating investigator, sponsor and QUANTA MEDICAL. Once approved the substantial amendment will be distributed for signature to all of the study investigators.

16.5. BENEFIT/RISK BALANCE

16.5.1. POTENTIAL BENEFITS

The use of the B-DYN device in the surgical treatment of lumbar stenosis could lead to maintaining the functional disability related to low back pain (preservation of walking ability and mobility) compared to fusion processing; it also helps maintain the level's mobility, while respecting the sagittal balance.

The hypothesis expresses that patients in the experimental group (B-DYN) will have less long-term adjacent syndrome compared to patients who have had a fusion.

16.5.2. POTENTIAL RISKS

This research does not entail any additional risk compared to the risk incurred during surgeries for the management of lumbar stenosis.

The complications are essentially those related to the surgical procedure:

- Complications of general anesthesia: these complications are detailed in the information sheet of the French Society of Anesthesia and Resuscitation, and are identical to those of any general anesthesia.
- Complications related to any surgery on the spine. We will mention infections, hemorrhage, pain, leakage of the cerebrospinal fluid, loss of neurological functions, etc. These complications will all be presented to you by your surgeon before the procedure. The treatment of these complications is well known and the investigative doctor knows how to take them in charge

Other complications that may arise are related to the medical device itself:

- Early or late loosening of any or all of the components

- Disassembly, bending and/or breakage of any or all of the components (screw breakage)
- Foreign body (allergic) reaction to implants, debris, corrosion products (from crevice, fretting, and/or general corrosion), including metallosis, tumor formation and/or autoimmune disease
- Pressure on the skin from components parts with inadequate tissue coverage over the implant possibly causing skin penetration, irritation, fibrosis, neurosis, and/or pain
- Tissue or nerve damage caused by improper positioning and placement of implants or instruments
- Post-operative change in spinal curvature, loss of correction, height, and/or reduction

17. PROCESSING OF DATA AND STORAGE OF RESEARCH DOCUMENTS AND DATA

17.1. DATA CIRCUIT

The **QUANTA** *VIEW*® application is:

- Modular;
- Multi-project;
- Multi-country, multi-lingual;
- Broadly configurable;
- Developed by Quanta Medical (proprietary application);
- Equipped with the functions needed for interventional and non-interventional studies.

QUANTA *VIEW*®

- Enables real-time project management from the centre-recruitment phase through to freezing of the database and study close-out;
- Brings together all stekeholders within a highly collaborative system based upon WorkFlow systems, by providing each with a pragmatic overview of actions to be performed and events to monitor.

QUANTA VIEW® comprises 3 modules:

- **QUANTA** VIEW® e-CRF or CDMS (Clinical Data Management System)
  - Open solution for data input by the investigators and for data management operations.
- **QUANTA** VIEW® CTMS (Clinical Study Management System)
  - Management of professionals;
  - Management of patients;
  - Logistical monitoring.
- **QUANTA** VIEW® CPMS (Collaborative Portal Management System) provides the following functions:
  - Progress indicators for the project;
  - Document access and sharing;

- Printout of status reports[2]:
  - monitoring of recruitment;
  - monitoring of patients by type;
  - monitoring of health care professionals;
  - monitoring of data management;
  - monitoring of logistics.

QUANTA VIEW® with its modularity can be readily adapted to projects and integrated wherever necessary into specific programs.
Version 5.300 of **QUANTA** VIEW® is in production on Quanta Medical servers hosted at the company site in Rueil-Malmaison.
QUANTA *VIEW* ® provides access for the the different project team members from:

- Quanta Medical;
- The Sponsor;
- The study centres.

The user guide, which is specifically dedicated to the study, is sent out prior to training of the investigators and staff allocated to data entry takes place.
This guide is available through the **QUANTA** VIEW® portal
User training is provided by the QM CRA during the set up visit.

Users are assisted through:

- A 2 level Hotline accessible through a toll-free number.

17.2. METHODS FOR PROCESSING, VERIFICATION AND VALIDATION OF DATA (DATA MANAGEMENT)

The study will be collected using a QUANTA VIEW The Clinical eBox electronic Case Report Form[3]
The data will be collected in real-time by the clinicians.
For this research, the subjects will be identified as follows: centre No. (3 numerical positions) - Selection order No. of the person in the centre (2 numerical positions) - surname initial - first name initial. This reference is unique and will be retained for the entire research period, in all documents necessary for the study, or by erasing (using suitable means) all the data on copies of documents source used for the research documentation.
The data management process is monitored in a QL (Quality Log) bringing together all key steps in the process. This QL also provides a medium for evaluation of the indicators applicable to the project.
There are 2 types of control:

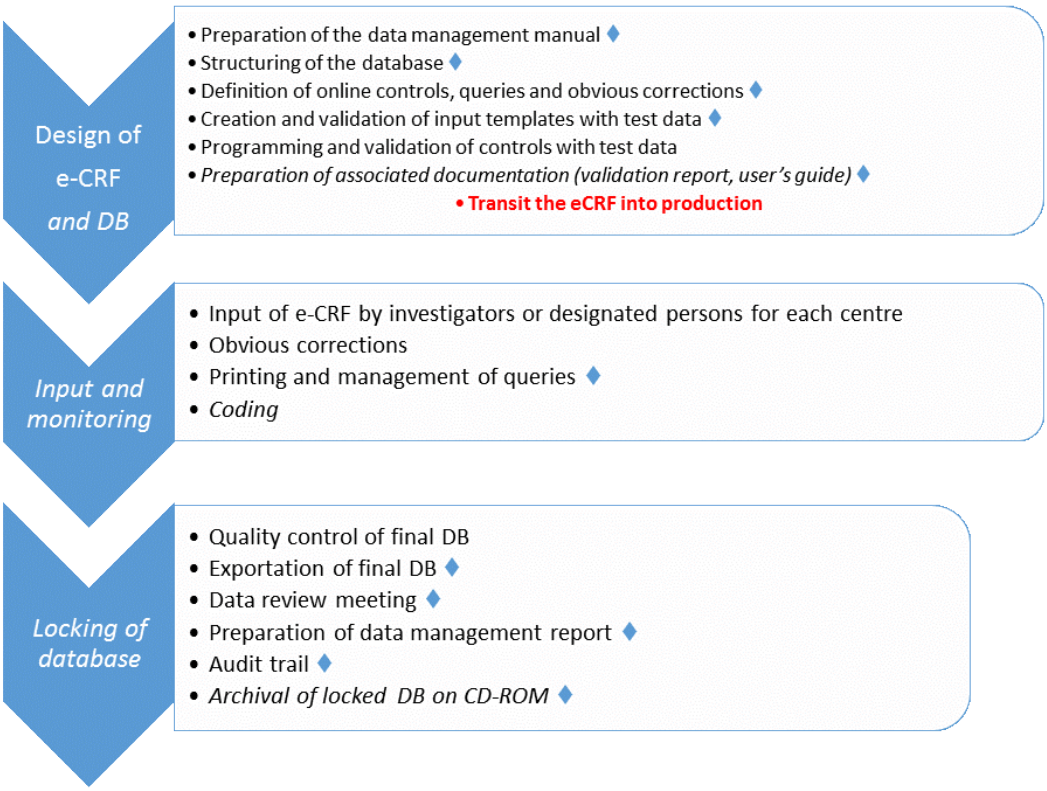
- Online checks during data entry by investigators with display of an error message in the event of any anomaly;
- Checks of the data entered enabling the generation of queries at specified intervals.

QUANTA VIEW The Clinical eBox ™ is a registered trademark of QUANTA MEDICAL™

in Excel format

3 QUANTA VIEW The Clinical eBox ™ is a registered trademark of QUANTA MEDICAL™

17.2.1. DATA MANAGEMENT



Data management process and actions (deliverables:)

In order to minimise the involvement of the investigators, QM proposes to set parameters for obvious corrections, which may be made with the agreement of the sponsor according to rules which will be defined in the Data-management manual.

17.2.2. BLIND REVIEW AND LOCKING OF THE DATABASE

The blind review will be prepared in order to present the patients and their data to the committee, which will then decide on classification of the deviations. The database will be locked after validation of the blind review repot.

17.3. ARCHIVING OF STUDY DOCUMENTS

It is the responsibility of the investigator to archive sufficient information about the identity of subjects taking part in the study in order to be able to provide these to the Health Authorities or sponsor if necessary.
The documents relating to the study are:

- The signed copy of the technical protocol;
- The investigator brochure;
- The financial agreement;
- The curricula vitae;
- The list of task delegations;

- The forms (originals), completed and signed, of the informed consent for each of the patients included;
- The copy of the Ethics Committee approval letter;
- The certification of insurance taken out by the sponsor;
- The copy of the data processing form (given to patient/returned to the investigator);
- The acknowledgements of receipt of the study materials;
- The list of patients included in the study (surnames, forenames, number and inclusion date, hospital file if applicable);
- The list of participating investigators;
- The copy of each patient's case report form or a print-out of patient data (document approved by the investigator);
- The originals of the original documents for each of the patients included;
- All correspondence relating to the study.

These documents must be stored for a minimum period of fifteen (15) years after the end of the study.

18. DATA OWNERSHIP - PUBLICATIONS OF RESULTS

It is agreed that the results of this study may not be presented in scientific meetings or published in scientific journals or on any other support without the prior written agreement of the sponsor. This also applies to any amendment which may be requested by an editor, review committee or editorial committee.
The members of the expert panel for this study may appear as co-authors of this publication
Will be first and last signatories of the publications, the person who really participated in the development of the protocol and its progress and the writing of the scientific article. Will also be signatories of the article investigators who included the number of patients required during the recruitment period.
The authors will jointly agree on the choice of the journal for the first publication to which they will grant rights for first publication.
. The sponsor reserves the right to use the results of this study in its medical information and to distribute reprints of publications.
The authors will accord their authorship copy right laws and rights of representation and reproduction, including translation into any language, on any support, by any means, worldwide, for any publications about this study.
Third parties may not use these rights without the prior written agreement of the sponsor.

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20. APPENDIX

20.1. STUDY FLOW CHART

Visits	V1 Inclusion	V2 intra- & post-op	V3 Follow up	V4 Follow up	V5 Follow up	Additional visits
Days / Data to be collected or Tests to be done		D0	M2 (± 7 d)	M12 (± 30 d)	M60 (± 60 d)	Consultation or hospitalisation
Information and signature of the consent	✓					
Medical history	✓					
History of the disease	✓					
Inclusion / non-inclusion criteria	✓					
Clinical test	✓	✓	✓	✓	✓	✓
Randomization and allocation of intervention	✓					
Intra-post-op. Immediat data collection		✓				
Case Report Form (CRF)	✓	✓	✓	✓	✓	✓
Oswestry Disability Index	✓		✓	✓	✓ (sup)	✓
Quality of life questionnaire (SF-12)	✓		✓	✓	✓ (sup)	
Motion and sensitivity assessment	✓		✓	✓	✓ (sup)	
VAS (low back pain and radicular pain)	✓	✓	✓	✓	✓ (sup)	
Anxiety (HAD score)	✓ (sup)		✓ (sup)	✓ (sup)	✓ (sup)	
Walking distance	✓		✓	✓	✓ (sup)	
MRI	✓			✓ (sup)	✓ (sup)	
Radiography (Télé-rachis or EOS)	✓		✓	✓	✓ (sup)	
Dynamic Radiograph	✓		✓	✓	✓ (sup)	✓
AE (Adverse event) collection		✓	✓	✓	✓	✓
Collect of concomitant treatments		✓	✓	✓	✓	✓

Supp : Additional tests compared to common practice

20.2. B-DYN DESCRIPTION

B-Dyn™

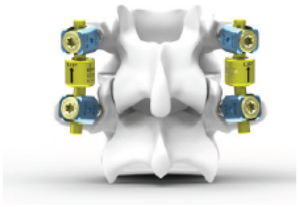
Posterior Dynamic Stabilization System

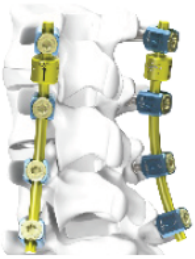
SHOCK ABSORBING MOTION PRESERVATION

B-Dyn™ is a posterior dynamic motion preservation system which is designed for application from thoracic vertebrae T10 to sacrum S1.

B-Dyn™ is supported by more than one thousand patients and clincal study results since 2008.

PRODUCT'S KEY POINTS





Motion preservation & control

B-Dyn™ allows all anatomical motion such as flexion/extension, axial rotation as well as lateral bending.

Shock absorption system

Silicone cushion helps to decrease intradiscal pressure and to relieve facet loads.
Elastomere ring controls hyper mobility and limits extension of the spine segment.

Fusion-motion **combined** solution

Beside a one level motion preservation device, B-Dyn™ has also a version with a longer fusion rod to combine 1 or 2 level fusion with motion preservation for the adjacent segment.

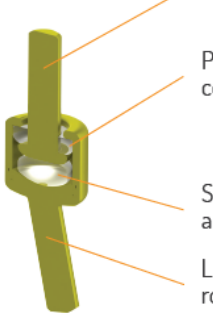
> INDICATIONS

- Degenerative intervertebral disc disease
- Spinal canal stenosis
- Degenerative spondylolisthesis grade 1
- Segmental instability

> MATERIAL

- Titanium
- Silicone
- PCU (Polycarbonate urethane)

> FEATURES



www.cousin-biotech.com

SHOCK ABSORBING MOTION PRESERVATION

> B-DYN

Spinal shock absorber

Size of B-Dyn	Small	Medium	Small	Medium
Diameter of rod	5.0 mm	5.0 mm	5.5 mm	5.5 mm
Reference	RCBDYSD50U	RCBDYMD50U	RCBDYSD55U	RCBDYMD55U

> POLYAXIAL PEDICLE SREWS

Length 30 to 55 mm

Diameter	5.5 mm	6.0 mm	6.5 mm	7.0 mm
Diameter of rod	5.0 mm			
Reference	RCB505530U	RCB506030U	RCB506530U	RCB507030U
	RCB505535U	RCB506035U	RCB506535U	RCB507035U
	RCB505540U	RCB506040U	RCB506540U	RCB507040U
	RCB505545U	RCB506045U	RCB506545U	RCB507045U
	RCB505550U	RCB506050U	RCB506550U	RCB507050U
	RCB505555U	RCB506055U	RCB506555U	RCB507055U

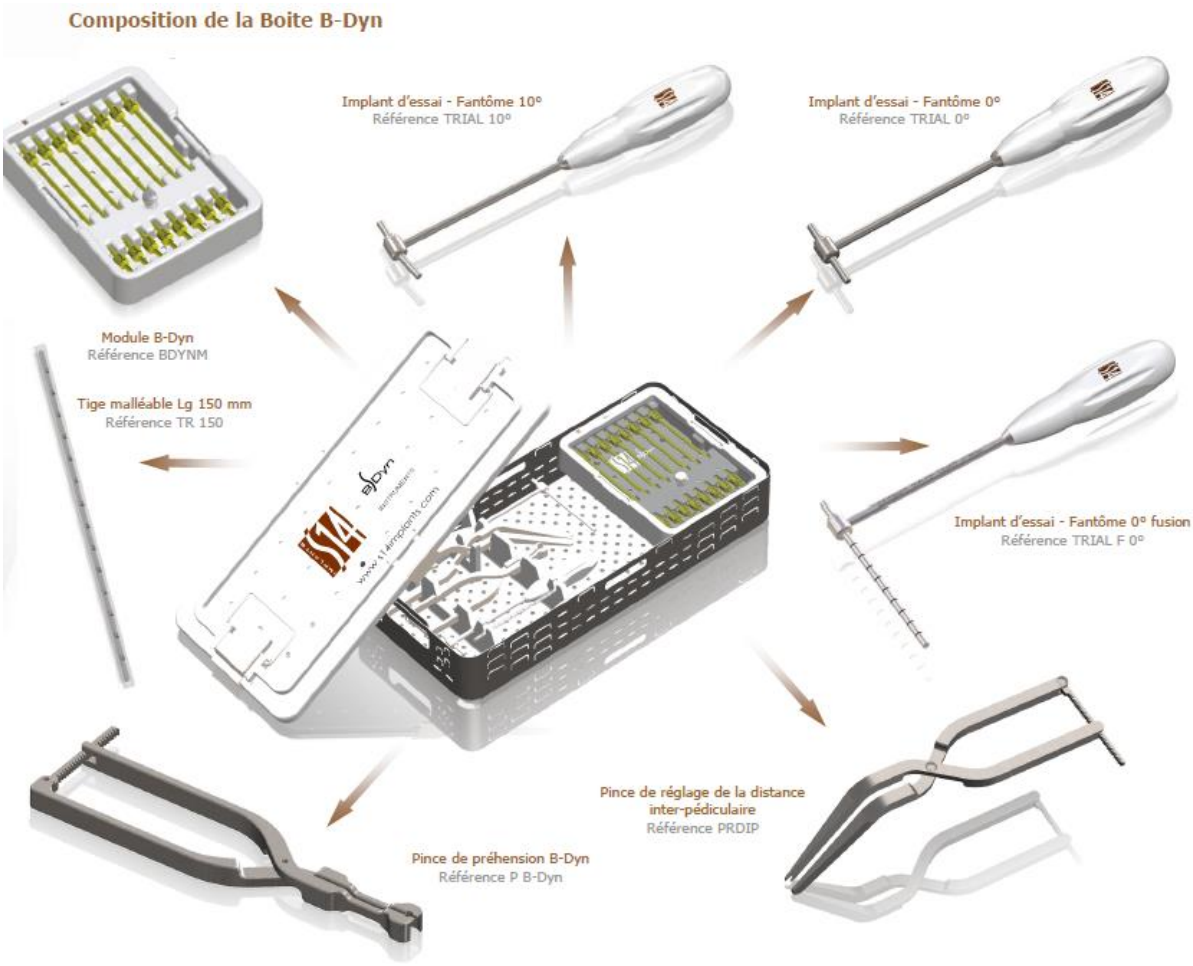
> REPLACEMENT RIGID RODS

5.0 mm diameter

Length	47 mm	107 mm
Reference	RCBFUL047U	RCBFUL107U
To replace	B-DYN SPINAL SHOCK ABSORBER: RCBDYSD50U	B-DYN SPINAL SHOCK ABSORBER: RCBDYMD50U

> ANCILLARIES

Reference	RCBKITDY50


Composition de la Boite B-Dyn
Implant d'essai - Fantôme 10°
Référence TRIAL 10°
Implant d'essai - Fantôme 0°
Référence TRIAL 0°
Module B-Dyn
Référence BDYNM
Tige malléable Lg 150 mm
Référence TR 150
Implant d'essai - Fantôme 0° fusion
Référence TRIAL F 0°
Pince de réglage de la distance inter-pédiculaire
Référence PRDIP
Pince de préhension B-Dyn
Référence P B-Dyn

20.3. INSTRUCTION FOR USE

Dispositif rachidien de stabilisation postérieure dynamique stérile

en	Instructions for use	Page	2
fr	Notice d'instructions	Page	6
de	Gebrauchsanweisung	Seite	10
it	Istruzioni per l'uso	Pagina	15
es	Instrucciones de uso	Pagina	20
pt	Nota de instruçoes	Pagina	24
nl	Gebruiksinstructies	Page	28
pl	Instrukcja obsługi	Strona	33
ru	Инструкция по	страница	38

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Fax : +33 (0) 3 20 14 40 13

www.cousin-biotech.com

Ancillaires CE

Implants BDyn CE 0120

Date de marquage CE: 17/11/2017

Made in France

NOT254 / 191011
Version du 11/10/2019

Rx only **Caution: Federal law (USA) restricts this device to sale, distribution and use by or on the order of a physician.**

This release is the last update of the instructions of use and replace the previous edition

Sterile spinal dynamic posterior stabilization device

1-DESCRIPTION

The sterile spinal dynamic posterior stabilization device BDyn is intended to restore the stabilization of the non-cervical segment of the spine by preserving the anatomical lordosis and the deadening of the intervertebral joint. It is composed of the BDyn spinal shock absorber fixed on the vertebrae thanks to the dedicated screws and can be replaced according to the decision of the surgeon by a dedicated replacement rigid rod.

2-MATERIALS

The B-DYN Device components are manufactured from medical grade titanium TA6V (ISO 5832-3; ASTM F 136), silicone, long-term implantable polyurethane.

BDyn Implant: Titanium alloy Ti6Al4V ELI (ISO 5832-3; ASTM F 136), Polydimethyl siloxane (PDMS) MED 4770 unrestricted
Polycarbonate urethane (PCU) Bionate® II 80A

BDyn ancillaries: Stainless steel, Titanium, Polypropylene

No human or animal origin – Non resorbable.

3-INDICATIONS

The sterile spinal dynamic posterior stabilization device BDyn is intended for posterior stabilization from thoracic vertebrae T10 to sacrum S1 with or without bone graft for the following indications:

- Degenerative intervertebral disc disease and/or articular facets confirmed by further examinations
- Spinal canal stenosis
- Degenerative spondylolisthesis grade 1
- Segmental instability

4-PERFORMANCE

The BDyn spinal shock absorber of the sterile spinal dynamic posterior stabilization device BDyn consists of a metallic cylindrical hollow part containing elastomer components made of silicone elastomers (polydimethyl siloxane (PDMS)) and long-term implantable polycarbonate urethane (PCU) which are bending out under the effect of a metallic piston rod connected with the vertebra of the treated segment by the pedicular screws tested and/or approved by the company COUSIN BIOTECH. The elastomer components assure the absorption of the mechanical loads applied on the intervertebral joint in compression, pulling, flexion-traction and lateral flexion. Some configurations enable fixation across several spinal segments.

5-CONTRAINDICATIONS

- Active infectious process or significant risk of infection (immunocompromise)
- Signs of local inflammation
- Fever or leukocytosis
- Morbid obesity
- Pregnancy
- Mental illness
- Grossly distorted anatomy caused by congenital abnormalities
- Any other medical or surgical condition which would preclude the potential benefit of spinal implant surgery, such as the presence of congenital abnormalities, elevation of the sedimentation rate unexplained by other diseases, elevation of the white blood count
- Suspected or documented metal allergy or intolerance
- Any case where the implant components selected for use would be too large or too small to achieve a successful result
- Any patient having inadequate tissue coverage over the operative site or inadequate bone stock or quality
- Any patient in which implant utilization would interfere with anatomical structures or expected physiological performance
- Any patient unwilling to follow postoperative instructions
- Any case not describe in the indications
- Traumas (i.e. fracture or dislocation)
- Abnormal curvatures (i.e. scoliosis and/or hyper lordosis)
- Tumors.
- Spondylolisthesis grade 2 and more
- Pseudarthrosis and/or failed previous fusion
- Severe bone resorption, osteomalacia, severe osteoporosis

6-UNDESIRABLE SIDE EFFECTS

All of the possible adverse events associated with spinal surgery and without instrumentation are possible:

- Infection
- Pseudomeningocele, fistula, breach dura, persistent CSF leakage, meningitis
- Loss of neurological function, sensorial and/or motor, including complete or incomplete paralysis, dysesthesias, hyperesthesia, anesthesia, paresthesia, appearance of radiculopathy, and/or the development or continuation of pain, numbness, neuroma, spasms, sensory loss, tingling sensation, and/or visual deficits
- *Cauda equina* syndrome, neuropathy, transient or permanent neurological deficits, paraplegia, paraparesis, reflex deficits, irritation, arachnoiditis, and/or muscle loss
- Urinary retention or loss of bladder control or other types of urological system compromise
- Scar formation possibly causing by a neurological compromise or compression around nerves and/or pain
- Fracture, microfracture, resorption, damage or penetration of any spinal bone (including the sacrum, pedicles, and/or vertebral body) and/or bone graft or bone graft harvest site at, above and/or below the level of surgery
- Herniated *nucleus pulposus*, disc disruption or degeneration at, above, or below the level of surgery, canal adjacent stenosis
- Non-union or pseudarthrosis, delayed union. Mal union
- Cessation of any potential growth of the operated portion of the spine
- Loss of or increase in spinal mobility or function
- Inability to perform the activities of daily living
- Bone loss or decrease in bone density
- Graft donor site complications including pain, fracture, or wound healing problems
- Ileus, gastritis, bowel obstruction or loss of bowel control or other types of gastrointestinal system compromise
- Hemorrhage, hematoma, occlusion, seroma, edema, hypertension, embolism, stroke, excessive bleeding, phlebitis, wound necrosis, wound dehiscence, damage to blood vessels, or other types of cardiovascular system compromise
- Reproduction system compromise, sterility, sexual dysfunction
- Development of respiratory problems, e.g. pulmonary embolism, atelectasis, bronchitis, pneumonia, etc
- Change in mental status

- Death

All of the possible adverse events associated with spinal surgery with instrumentation are possible. A listing of potential adverse events linked to the medical device includes, not limited to:
- Early or late loosening of any or all of the components
- Disassembly, bending and/or breakage of any or all of the components (screw breakage)
- Foreign body (allergic) reaction to implants, debris, corrosion products (from crevice, fretting, and/or general corrosion), including metallosis, tumor formation and/or autoimmune disease
- Pressure on the skin from components parts with inadequate tissue coverage over the implant possibly causing skin penetration, irritation, fibrosis, neurosis, and/or pain
- Tissue or nerve damage caused by improper positioning and placement of implants or instruments
- Post-operative change in spinal curvature, loss of correction, height, and/or reduction

7-PRECAUTIONS FOR USE

The BDyn devices are delivered sterile, sterilized by ethylene oxide.
Before any use, inspect the integrity of the packaging and device (including peelable pouches).
Do not use in the event of deterioration of the labels and/or the device and/or the packaging.
Do not use if the device is out of date.
The sterile spinal dynamic posterior stabilization device BDyn is only intended to adult human female or male more than 40 Kg.
COUSIN BIOTECH does not offer any guarantee or recommendation as far as the use of a particular type of means of fixation is concerned.
The installation of BDyn device can only be made with pedicular screws tested and/or approved by the company COUSIN BIOTECH.
The eventual substitution of the BDyn spinal shock absorber has to be carried out only with the dedicated replacement rigid rods.
You should never use implants made of stainless steel and titanium alloy in the same construct.
A successful result is not always achieved in every surgical case. This fact is especially true in spinal surgery where many extenuating circumstances may compromise the results. This device system is not intended to be the sole means of spinal support. No spinal implant can withstand body loads without the support of bone. In this event, bending, loosening, disassembly and/or breakage of the device(s) will eventually occur.
Preoperative and operating procedures, including precise knowledge of suitable surgical techniques, and proper selection of the good reference of the device adapted to the patient and its narrow setting up are important considerations in the successful use of the device by the surgeon.
The BDyn device must be implanted only by a qualified surgeon, having knowledge in the use of the product and who has the knowledge of the anatomy, spinal surgery, pedicle screws fixation technique and specific BDyn device surgical technique
Postoperative precautions

MRI safety

The implants are composed of non-ferromagnetic materials and present a geometry non susceptible to generate induced currents. Moreover, as they are fixed to bone /or/ tissues, they are unlikely to be mobilised. A priori they can be considered compatible with an MRI scan. Their safety, in particular in terms of heating and migration of implant has been evaluated through bibliographic data by comparison with data available on devices with similar composition, shape and use. This evaluation concluded to a safety use for MRI scan between 1.5 and 3 Tesla.
As a precautionary measure, it is recommended to avoid MRI scans within the 48h of the implant placement, and to inform the person in charge of the scan of the recent implant placement, if such examination is essential.
It has to be noted that the devices which present a high contrast with the biological environment can generate « artifacts » that has to be taken into account for the perfect execution and interpretation of imaging exams.
For this purpose, it has to be recommended to the patient who has this implant to warn as far as possible the concerned health professionals (radiologists and radiology operators) about the presence of this implant before these exams.

IMPORTANT: DO NOT REUSE - DO NOT RESTERILIZE

In accordance with the labelling of this product, BDyn implants are for single use; they must not in any case be reused or re-sterilised (potential risks include, but are not limited to, loss of sterility of the products, risk of infection, loss of product efficacy, recurrence, etc.)

8-SURGICAL TECHNIQUE

The placement of the spinal dynamic posterior stabilization device BDyn begins by the preparation of the pedicles of the vertebrae and by the pedicle aim and the fixation of the pedicle screws.

When tapping the vertebrae to prepare the hole before the insertion of the pedicle screw, flexion efforts on the tap are to be avoided. It must stay in the lined-up in order to make as straightest a pre-hole as possible to ensure as secure a screw placement as possible, with a straight guidance way. Thus, when tapping the vertebrae in order to stay in the line-up and to create a straight pre-hole.

Viewed in the sagittal plane, the pedicle screws must be as parallel as possible in order to let the biggest available space to place the cylindrical body of BDyn spinal shock absorber and facilitate its insertion between the head of the polyaxial pedicle screws. It is preferable to be sure that the adequate implant, with an appropriate size is used with the instrumentation which suit. A 2 mm space between the top of the cylindrical body of the BDyn spinal shock absorber and the lower part of the screw head must be respected to insure the shock absoption stock necessary for the good working of the BDyn device. For that, the surgeon can use the trial device RCBANTD50U to check if there is enough space to place the BDyn spinal shock absorber.
The mobile piston rod of the BDyn spinal shock absorber must be fixed in the head of the screw concentrically to the cylindrical body.

The surgery ends by the final tightening by using the dedicated torque limiting of the plugs on the head of the polyaxial pedicle screws by using systematically the suitable antirotator.

It is important to manipulate correctly the implants. The components of the implants to be arched do not have to be against-arched in the opposite direction. In any case they have to be chipped. These operations could effectuate the concentration of internal stresses which could become the place of an eventual failure of the implant.

9-PRESENTATION AND WARNING ABOUT ANCILLARIES

- The BDyn ancillaries are Class I medical devices, intended for temporary use and are re-usable.
Unlike the BDyn implants, the ancillaries included in the instrument set are furnished non sterile.
Before use, the ancillaries must be:
- cleaned by the appropriate mode of cleaning
- sterilized in an autoclave by moist heat
After use, the ancillaries have to be cleaned and decontaminated according to a suitable protocol especially by taking into account the reduction of the risk of transmission of unconventional transmissible agents - UTA.
In case of a patient suspected of having Creutzfeld-Jacob Disease (CJD), perform suitable decontamination.
In the event of a confirmed case of CJD, incinerate the ancillaries.

10-DECONTAMINATION AND CLEANING OF BDYN ANCILLARIES

Decontamination and cleaning are performed under the responsibility of the healthcare centers.
The following prescribed methods and materials must be used to reduce the risk of transmission of UTA, (French health ministry - DGS/R13/2011/449 dated 01/12/2011).

This step has to take place before **the first utilization** and **immediately after the utilization** to avoid adhesion of particles or dry secretion to the instruments
The detachable instruments have to be dismantled

Products advised for the cleaning
- an enzymatic detergent neutral
- Or products adapted for the cleaning (neutral or soft alkaline) of chirurgical instruments in compliance with the reglementation in effect.

- **Warning:** Don't use corrosive factor or caustic cleaning product

2 process are possible

A- **Chart Automated cleaning in a disinfector washer with manual Pre-cleaning:**

	Step	Step Description	Step Instruction	Accessories	Duration
Cleaning Steps	1	Contamination Removal	Rinse product room temperature running tap water removing any visible organic metarial witn assistance of a soft bristle brush	- Tap water - Soft bristle brush **(Do not utilize metal cleaning brushes)**	Until all visible soi lis removed
	2	Pre-soak	Prepare a detergent solution at ambient température (15-25°C / 59-77°F). Afterwards lumina, threads, joints and gaps of the instruments have to be flushed with a water jet pistol for a minimum time of 10 seconds for each position.	- Detergent - Water jet pistol	Until product is visually clean
	3	Ultrasonic cleaning	Clean the instrument in the ultrasonic tray including the solution. **Be careful every unclench connector or screws and bolts by the vibrations will be reassure.**	- Ultrasonic tray	Minimum duration 10 minutes, this duration can vary according product
	4	Soak	Soak the instrument in tap water during 30 seconds. After, ultrasonic treatment the lumina, threads, joints and gaps of the instrument have to be flushed again with a water jet pistol for a minimum time of 10 seconds for each position.	- Reserve osmosis water	Minimum 30 seconds of soak
	5	Automated Washer	Place entire disassembled device into the automated washer	- Automated Washer - Disassembled Device	Minimum total cycle time: 39 minutes

Instructions of cleaning in washer / disinfector			
Cycles parameters	Time	Minimum temperature	Type of detergent/water
Pre-cleaning	2 minutes	<45°C / <113°F	Tap water
Cleaning	5 minutes	55°C / 131°F	Detergent
Draining	2 minutes	<45°C / <113°F	Tap water
Thermic draining	5 minutes	90°C / 194°F	Reserve osmosis water
Drying	25 minutes	> 70°C / > 158°F	Not applicable

Finishing Steps	6	Final Rinse	**Rinse** carefully with **distilled water**	- Distilled water	Minimum 1 minute
	7	Final Drying	**Dry** devise utilizing medical quality filtered air	- Medical quality filtered air	Until product is visually dry
	8	Tidying	The instruments have to be placed **in the right position** inside the trays as described **on the position map fixed** on the tray for the sterilization.		

B- **Chart Just manual cleaning :**

	Step	Step Description	Step Instruction	Accessories	Duration
Cleaning Steps	1	Contamination Removal	Rinse product room temperature running tap water removing any visible organic metarial witn assistance of a soft bristle brush	- Tap water - Soft bristle brush **(Do not utilize metal cleaning brushes)**	Until all visible soi lis removed
	2	Drying	Dry the device utilizing a dry non-shedding wipe. Medical quality filtered air may be utilized if available	- Non-schedding wipe - Medical quality filtered compressed air	Until product is visually dry
Disinfection Steps	3	Disinfection Application	Prepare a low-foaming neutral enzymatic detergent solution, using tap water (15-25°C / 59-77°F). Soak the instrument in the open position (if possible) during minimum 1 minute. During the immersion, actuate mobile parts of the instrument minimum 3 times (if possible),so that the detergent can access all parts of the instrument.	- Detergent	Minimum duration 1 minute, this duration can vary according product
	4	Drying	After the soaking time, take out the instrument and wipe it with a disposable cloth. Then, place the instrument in a new bath of enzymatic detergent solution using warm tap water.	- Disposable cloth - Detergent	Until product is visually dry
	5	Manual Disinfection	Brush all surface of the instrument using a soft brush for 2 minutes. Adjust brushing time if needed. Actuate mobile parts of the instrument 3 times (when	- Soft bristle brush - Detergent - Syringe	Manual cleaning time duration is complete when the device's surface,

			applicable) and use a syringe to access all difficult areas. Use a volume of 60 mL of the detergent solution.		joints, and crevices have been manully cleaned

Disinfection Steps	6	Rinse and finition	Soak the instrument in reverse osmosis water for 1 minute. Use a syringe and 60mL of reverse osmosis water to access all difficult areas. Repeat soaking 2 additional times using fresh water	- Reserve osmosis water - Syringe	Minimum 1 minute
	7	Final Rinse	**Rinse** carefully with **distilled water**	- Distilled water	Minimum 1 minute
	8	Final Drying	**Dry** devise utilizing medical quality filtered air	- Medical quality filtered air	Until product is visually dry
	9	Tidying	The instruments have to be placed **in the right position** inside the trays as described **on the position map fixed** on the tray for the sterilization.		

Note: In case of **suspection** of **Creutzfeld-Jakob Disease** (CJD), incinerate the ancillaries and the fixation pliers
In case of non respect of the instructions mentioned above, the healthcare center will have to apply a validated equivalent cleaning process for which it will be fully responsible.

11-STERILIZATION OF BDYN ANCILLARIES
Sterilization is performed under the responsibility of the healthcare centers.
The following prescribed method and materials must be used to reduce the risk of transmission of UTA, (French health ministry - DGS/R13/2011/449 dated 01/12/2011).
In case of non respect of the instructions mentioned above, the healthcare center will have to apply a validated equivalent cleaning process for **which it will be fully responsible.**

1- The sterilization in autoclave is to make in a **specific container** (fenced basket, Tray, Plastic tray placed in a peelable pouches autoclavable).

NB: It **isn't recommended** to realize the sterilization with peelables pouches ***autoclavables*** without a container ➔ Ancillaries can pierce the films components the pouches.

2-A sterilization **BY AUTOCLAVE** is advised following this protocol:

Steam sterilization parameters	Values
Cycle Type	Pre-vacuum
Set Point Temperature	134°C / 273°F
Cycle Time	Minimum 3 minutes
Dry Time	Minimum 30 minutes
Cool Time (inside and outside the autoclave chambers)	Minimum 40 minutes

3 - Remark: After each cycle of cleaning/sterilization, insure of all the good working of the ancillaries: verify the integrality and the correct operation, of the locking systems (clipping, prehension) without excessive play.

4- If the ancillaries utilization is different, after sterilization stock them in a tray on a peelable pouches.

In case of non respect of the instructions mentioned above, the healthcare center will have to apply a validated equivalent cleaning process for which it will be fully responsible.

12-STORAGE PRECAUTIONS
- The BDyn devices must be stored in a clean, dry and tempered place under atmospheric pressure, away from sunlight and rays in its original packaging. Ensure that the box is not dropped, hit or crushed.
- The ancillaries must be stored in a dedicated container or equivalent packaging to prevent any deterioration.

13-EXPLANTATION AND ELIMINATION OF DEVICES
Explantation and handling should be done following recommendations of ISO 12891-1:2015 « Implants for surgery – Retrieval and analysis of surgical implants » Part 1: « Retrieval and Handling ».
Any explanted device must be send back, for analysis, following the current protocol. This protocol is available on demand to COUSIN BIOTECH. It is important to note that any implant that should not have been cleaned and disinfected before expedition must be contained in a sealed package.
The elimination of explanted medical device must be conducted in accordance with standards in the country for the disposal of infectious hazards waste.
The elimination of a non-implanted device is not the subject of specific recommendations.
The surgeon will decide the necessity of the resection of the BDyn, its replacement or the rachis fusion according to the known and recognized techniques.

14-INFORMATION REQUEST AND CLAIMS
Following its quality policy, COUSIN BIOTECH is committed to make every effort to produce and supply a high quality medical device. However, if a health professional (client, user, prescriber ...) had a claim or cause of dissatisfaction with a product in terms of quality, safety or performance, he must inform COUSIN BIOTECH as soon as possible. In case of failure of an implant or if it contributed to cause serious adverse effects for the patient, the healthcare center must follow the legal procedures in his country, and inform COUSIN BIOTECH in the shortest time. For any correspondence, thank you to specify the reference, batch number, the coordinates of a reference and a comprehensive description of the incident or claim. Brochures, documentation and surgical technique are available on request from COUSIN BIOTECH and its distributors. If further information is needed or required, please contact your COUSIN BIOTECH representative or distributor.

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20.4. SURGICAL PROCEDURE

20.5. CE MARKED CERTIFICATE

EC Certificate Full Quality Assurance System: Certificate/Certificat FR96/8324

The management system of / Le système de management de

COUSIN BIOTECH s.a.s.

8, Rue de l'Abbé Bonpain, 59117 Wervicq-Sud, France

has been assessed and certified as meeting the requirements of
a été audité et certifié selon les exigences de

Directive 93/42/EEC

on medical devices, Annex II (excluding Section 4)

Directive 93/42/EEC

Dispositifs médicaux, Annexe II (section 4 exclue)

For the following products / Pour les produits suivants

The scope of registration appears on page 2 of this certificate.
Le domaine de certification apparaît en page 2 de ce certificat.

This certificate is valid from 23 May 2018 until 03 May 2021
and remains valid subject to satisfactory surveillance audits.
Re certification audit due before 02 May 2019
Issue 39. Certified since 31 October 1996
Le certificat est valable du 23 mai 2018 au 03 mai 2021
et reste valide jusqu'à décision satisfaisante à l'issue des audits de suivi.
L'audit de renouvellement doit avoir lieu avant 02 mai 2019
Version 39. Certifié depuis 31 octobre 1996

Certification is based on reports numbered FR/MD 06953
Cette certification est basée sur les rapports numérotés FR/MD 06953

This is a multi-site certification.
Additional site details are listed on subsequent pages.
Ceci est une certification multisite.
La liste des sites additionnels est mentionnée dans les pages suivantes.

Authorised by/Autorisé par

SGS United Kingdom Ltd, Notified Body 0120
202B Worle Parkway, Weston-super-Mare, BS22 6WA UK
t +44 (0)1934 522917 f +44 (0)1934 522137 www.sgs.com

SGS CE 02 0315 M4 FR

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COUSIN BIOTECH s.a.s.

Directive 93/42/EEC

on medical devices, Annex II (excluding Section 4)

Directive 93/42/EEC

Dispositifs médicaux, Annexe II (section 4 exclue)

Issue / Version 39

Detailed scope/Domaine d'activité détaillé

Non resorbable extraperitoneal parietal reinforcement sterile implants (Abdominal plug and meshes and reinforcement plug and meshes abdominal wall); Sterile Adjustable gastric banding; Sterile Non resorbable articular ligaments; Sterile Anchor devices; Sterile Devices for the interspinous space (with spinous support or with laminar support); Sterile Intervertebral prostheses; Sterile Urogenital implants (Suburethral support tape and Implant for the treatment of prolapse); Non-sterile Trial Prosthesis for spinal and visceral surgeries; Sterile ligament system for spine stabilization; Sterile spinal dynamic posterior stabilization devices.

Sterile Adhesix® Parietal Reinforcement Meshes with one adhesive side; Sterile Semi Resorbable Meshes, Plugs and Films: 4DMESH®, 4DDOME®, 4D VENTRAL®, Biomesh® CA.B.S.'Air ® SR, Semi Resorbable Reinforcement Parietal Implant; Sterile Neurological Patches: Biomesh™ N3 and N3L, Cranial and Spinal Dura Mater Substitutes; Sterile Adjustable gastric banding with adhesive mesh support for the implantable port Adhesix® Bioring®.

Class I Sterile: "Sterility aspects only - Restricted to the aspects of manufacture concerned with securing and maintaining sterile conditions".

**Sterile Non implantable medical devices for spinal surgery comprising:
Ligament system for spinal stabilization.**

COUSIN BIOTECH s.a.s.

Directive 93/42/EEC

on medical devices, Annex II (excluding Section 4)

Directive 93/42/EEC

Dispositifs médicaux, Annexe II (section 4 exclue)

Issue / Version 39

Implants stériles de renforcement pariétal extrapéritonéale non résorbables (plaques et plugs abdominaux et plaques et plugs de renforcement de la paroi abdominale); Anneaux gastriques ajustables stériles; Ligaments articulaires non résorbables stériles; Ligaments élastiques non résorbables stériles; Dispositifs d'ancrage stériles; Dispositifs stériles pour l'espace inter épineux (avec appui épineux ou avec appui lamaire); Prothèses intervertébrales stériles; Implants urogénitaux stériles (Bandelettes de support sous urétrales et Implants pour le traitement du prolapsus); Prothèses d'essai non-stériles pour les chirurgies rachidienne et viscérale; Système ligamentaire stérile pour stabilisation rachidienne; Dispositifs rachidiens stériles de stabilisation postérieure dynamique.

Adhesix® Implants de renforcement pariétal adhésifs stériles; Plaques, Plugs et Films semi résorbables stériles: 4DMESH®, 4DDOME®, 4D VENTRAL® and Biomesh® CA.B.S.'Air SR®, Implant de renforcement pariétal semi résorbable; Patchs neurologiques stériles Biomesh® N3 et N3L, Substituts de la dure mère crânienne et spinale; Anneau gastrique ajustable stérile avec système de fixation adhésif de la chambre implantable Adhesix® Bioring®.

Classe I stérile: « Aspects stérilité uniquement – Restreint aux seuls aspects de la fabrication visant à garantir et maintenir la stérilité ».

Dispositifs médicaux non implantables stériles pour la chirurgie rachidienne comprenant: Système ligamentaire pour stabilisation rachidienne.

Where the above scope includes class III medical device(s), a valid EC Design Examination Certificate according to Annex II (Section 4) is a mandatory requirement for each device in addition to this certificate to place that device on the market

Lorsque le périmètre ci-dessus inclus un Dispositif Médical de classe III, un certificat d'examen CE de Conception (ECDE) suivant l'annexe II (section 4) valide, en addition du présent certificat est une exigence obligatoire pour la mise sur le marché de chaque dispositif

Additional facilities/Sites additionnels

Allée des Roses, 59117 Wervicq-Sud, France

20.6. OSWESTRY DISABILITY INDEX

Oswestry Disability Index 2.0

Name _____ Date _____ Score: _____

Please Read: Could you please complete this questionnaire. It is designed to give us information as to how your back (or leg) trouble has affected your ability to manage in everyday life

Please answer every section. Circle only one in each section that most closely describes you **today.**

Section 1 - Pain Intensity A. I have no pain at the moment B. The pain is very mild at the moment C. The pain is moderate at the moment D. The pain is fairly severe at the moment E. The pain is very severe at the moment F. The pain is the worst imaginable at the moment	**Section 6 - Standing** A. I can stand as long as I want without extra pain B. I can stand as long as I want but it gives me extra pain C. Pain prevents me from standing for more than 1 hour D. Pain prevents me from standing for more than 1/2 hour E. Pain prevents me from standing for more than 10 minutes F. Pain prevents me from standing at all
Section 2 - Personal care (washing, dressing, etc) A. I can look after myself normally without extra pain B. I can look aftr myself normally but it is very painful C. It is painful to look after myself and I am slow and careful D. I need some help but manage most of my personal care E. I need help everyday in most aspects of self care F. I do not get dressed, wash with difficulty and stay in bed	**Section 7 - Sleeping** A. My sleep is never disturbed by pain B. My sleep is occasionally disturbed by pain C. Because of pain, I have less than 6 hours of sleep D. Because of pain, I have less than 4 hours of sleep E. Because of pain, I have less than 2 hours of sleep F. Pain prevents me from sleeping at all
Section 3 - Lifting A. I can lift heavy weights without extra pain B. I can lift heavy weights, but it causes extra pain C. Pain prevents me from lifting heavy weights off the floor but I can manage if they are conveniently positioned D. Pain prevents me from lifting heavy weights but I can manage light/medium weights if they are conveniently positioned E. I can only lift very light weights at the most F. I cannot lift or carry anything at all	**Section 8 - Sex Life** A. My sex life is normal and causes me no extra pain B. My sex life is normal, but causes some extra pain C. My sex life is nearly normal but is very painful D. My sex life is severly restricted by pain E. My sex life is nearly absent because of pain F. Pain prevents any sex life at all
Section 4 - Walking A. Pain does not prevent me from walking any distance B. Pain prevents me from walking more than 1 mile C. Pain prevents me from walking more than 1/4 mile D. Pain prevents me from walking more than 100 yards E. I can only walk while using a stick or crutches F. I am in bed most of the time and have to crawl to the toilet	**Section 9 - Social Life** A. My social life is normal and causes me no extra pain B. My social life is normal, but increases the degree of pain C. Pain has no significant effect on my social life apart from limiting my more energetic interests (sports, etc) D. Pain has restricted my social life and I do not go out as often E. Pain has restricted my social life to home F. I have no social life because of the pain
Section 5 - Sitting A. I can sit in any chair as long as I like B. I can only sit in my favorite chair as long as I like C. Pain prevents me from sitting more than 1 hour D. Pain prevents me from sitting more than 1/2 hour E. Pain prevents me from sitting more than 10 minutes F. Pain prevents me from sitting at all	**Section 10 - Traveling** A. I can travel anywhere without pain B. I can travel anywhere but it causes extra pain C. Pain is bad but I manage journeys over 2 hours D. Pain restricts me to journeys of less than 1 hour E. Pain restricts me to short necessary journeys under 30 min. F. Pain prevents me from traveling except to receive treatment

Comments: _____

Roland, M. and J. Fairbank (2000). "The Roland-Morris Disability Questionnaire and the Oswestry Disability Questionnaire." Spine 25(24)3115-24

20.7. SF-12

SF-12v2™ Health Survey

(SF-12 v2 Standard, US Version 2.0)

Identification Number
Event

To be completed by the PATIENT

Directions: *This survey asks for your views about your health. This information will help you keep track of how you feel and how well you are able to do your usual activities. If you need to change an answer, completely erase the incorrect mark and fill in the correct circle. If you are unsure about how to answer a question, please give the best answer you can.*

Today's Date (MM/DD/YY) ☐☐ / ☐☐ / ☐☐

Shade circles like this: ● **Not like this:** ⊗ ✓

Mark only one answer for each question. Please do not mark outside the circles or make stray marks on the questionnaire.

01. In general, would you say your health is:	Excellent ○	Very Good ○	Good ○	Fair ○	Poor ○

The following questions are about activities you might do during a typical day. Does your health now limit you in these activities? If so, how much?	Yes, limited a lot	Yes, limited a little	No, not limited at all
02. Moderate activities, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf	○	○	○
03. Climbing several flights of stairs	○	○	○

During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of your physical health?	All of the time	Most of the time	Some of the time	A little of the time	None of the time
04. Accomplished less than you would like	○	○	○	○	○
05. Were limited in the kind of work or other activities	○	○	○	○	○

During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)?	All of the time	Most of the time	Some of the time	A little of the time	None of the time
06. Accomplished less than you would like	○	○	○	○	○
07. Did work or activities less carefully than usual	○	○	○	○	○

08. During the past 4 weeks, how much did pain interfere with your normal work (including both work outside the home and housework)?	Not at all ○	A little bit ○	Moderately ○	Quite a bit ○	Extremely ○

These questions are about how you feel and how things have been with you during the past 4 weeks. For each question, please give the one answer that comes closest to the way you have been feeling. How much of the time during the past 4 weeks…	All of the time	Most of the time	Some of the time	A little of the time	None of the time
09. Have you felt calm and peaceful	○	○	○	○	○
10. Did you have a lot of energy	○	○	○	○	○
11. Have you felt downhearted and depressed	○	○	○	○	○
12. During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting friends, relatives, etc.)?	○	○	○	○	○

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20.8. NEUROLOGICAL AND MOTOR STATUS ASSESSMENT

Neurological and motor status

Motor deficit (MRC scale)

L4		L5		S1	
Left	**Right**	**Left**	**Right**	**Left**	**Right**
☐ 0	☐ 0	☐ 0	☐ 0	☐ 0	☐ 0
☐ 1	☐ 1	☐ 1	☐ 1	☐ 1	☐ 1
☐ 2	☐ 2	☐ 2	☐ 2	☐ 2	☐ 2
☐ 3	☐ 3	☐ 3	☐ 3	☐ 3	☐ 3
☐ 4	☐ 4	☐ 4	☐ 4	☐ 4	☐ 4
☐ 5	☐ 5	☐ 5	☐ 5	☐ 5	☐ 5

Grade	Motor Function
0	No movement or contraction
1	Trace movement or fasciculations
2	Active motion with gravity eliminated
3	Active motion against gravity only
4	Active motion against some resistance
5	Full strength

Sensory assessment

Light touch

L4		L5		S1	
Left	**Right**	**Left**	**Right**	**Left**	**Right**
☐ 0 : Absent ☐ 1 : Altered ☐ 2 : normal	☐ 0 : Absent ☐ 1 : Altered ☐ 2 : normal	☐ 0 : Absent ☐ 1 : Altered ☐ 2 : normal	☐ 0 : Absent ☐ 1 : Altered ☐ 2 : normal	☐ 0 : Absent ☐ 1 : Altered ☐ 2 : normal	☐ 0 : Absent ☐ 1 : Altered ☐ 2 : normal

Pin Prick

L4		L5		S1	
Left	**Right**	**Left**	**Right**	**Left**	**Right**
☐ 0 : Absent ☐ 1 : Altered ☐ 2 : normal	☐ 0 : Absent ☐ 1 : Altered ☐ 2 : normal	☐ 0 : Absent ☐ 1 : Altered ☐ 2 : normal	☐ 0 : Absent ☐ 1 : Altered ☐ 2 : normal	☐ 0 : Absent ☐ 1 : Altered ☐ 2 : normal	☐ 0 : Absent ☐ 1 : Altered ☐ 2 : normal

20.9. HAD SCALE

Hospital Anxiety and Depression Scale (HADS)

Tick the box beside the reply that is closest to how you have been feeling in the past week.
Don't take too long over you replies: your immediate is best.

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

Please check you have answered all the questions

Scoring:
Total score: Depression (D) _____ Anxiety (A) _____
0-7 = Normal
8-10 = Borderline abnormal (borderline case)
11-21 = Abnormal (case)

20.10. SERIOUS ADVERSE EVENT (SAE) RECORDING FORM

	Form for the notification of a serious adverse event (SAE) occurring during Research on a Human Being ***Medical device***	BOX RESERVED FOR SPONSOR DATE OF RECEIPT: ___ /_____ /_____ SAE N° |__|__|__|

Initial notification ☐ **SAE follow-up** ☐

1. Identification of the research	
Acronym:	**BDYNCLIN**
Research number:	2834_BDYNCLIN
Full title of the research involving Human Beings:	**"Study of the efficacy and tolerance of the B-Dyn medical device compared to a conventional bolted fusion with or without cage in the treatment of degenerative lumbar stenosis, with or without grade I spondylolisthesis on the degree of postoperative functional disability, preservation of mobility and prevention of the adjacent syndrome".** *Interventional, prospective, comparative, randomized, non-inferiority, single blind, international, multicenter clinical study***.**

2. Identification of the centre
Institution name: ..... Town and post code: ..... Department: .....

3. Identification and past history of the person taking part in the research	
Patient N°:	|__|__|__| - |__|__| - |__| - |__| Centre No. – patient selection no. – initials – initial surname, forename
Sex:	☐ M ☐ F
Weight:	|__|__|__| kg
Height:	|__|__|__| cm
Date of birth:	|__|__| |__|__| |__|__|__|__| dd mm yyyy
Past medical and surgical history	.....
Date of signature of consent:	|__|__| |__|__| |__|__|__|__| dd mm yyyy
Date of randomisation:	|__|__| |__|__| |__|__|__|__| dd mm yyyy
Randomisation arm	☐ BDYN ☐ Fusion

4. Surgical procedure before the development of the SAE *(delete box if treatment not started)*		
	Date of the procedure *(dd/mm/yyyy)*	Batch no.
BDYN ☐	|__|__| |__|__| |__|__|__|__|	……
Fusion ☐	|__|__| |__|__| |__|__|__|__|	

5. Serious adverse event [SAE]	
Name:	……
Description:	……
Body site	……
Date of onset of the SAE:	|__|__| |__|__| |__|__|__|__| dd mm yyyy
Severity	☐ Death: |__|__| |__|__| |_2_|_0_|__|__| ☐ Life-threatening for patient ☐ Important medical event ☐ Hospitalisation (initial or prolonged): from |__|__| |__|__| |_2_|_0_|__|__| to |__|__| |__|__| |_2_|_0_|__|__| ☐ ongoing ☐ Disability or incapacity ☐ Other(s) , give details: ……
Did the patient receive any treatment for this SAE?	☐Yes ☐No If yes, specify: Medical ☐Yes ☐No If medical treatment specify: …… Surgical ☐Yes ☐No If surgical treatment, specify measures taken regarding the device ☐ Removal ☐ Total replacement ☐ Re-adjustment ☐ Other If other, specify procedures performed: …… Date of surgery: |__|__| |__|__| |_2_|_0_|__|__|
Outcome of event	
☐ **Resolved:** ○ without sequelae ○ with sequelae, specify which:	Date: |__|__| |__|__| |__|__|__|__| dd mm yyyy duration if < 24 h |__|__| h |__|__| min
☐ **Not resolved (ongoing)**, specify: ○ Stable state ○ Improved ○ Deteriorated	

☐ **Death** ○ unrelated to the SAE ○ related to the SAE ☐ **Not assessable**	Date of death: |__|__| |__|__| |__|__|__|__| dd mm yyyy	
Place of onset	☐ Home ☐ Day hospital ☐ Hospital ☐ Convalescence home	

6. In the opinion of the investigator, is the serious adverse event (several options possible)
related to the research medical device? ☐ Unlikely ☐Possible ☐ Probable ☐Certain **related to the surgical procedure**? ☐ Unlikely ☐Possible ☐ Probable ☐Certain **related to another event:** ☐Yes ☐No If yes, specify: progression of the disease on which the research was being conducted ☐Yes ☐No to one (or more) concomitant medicinal product(s) ☐Yes ☐No if yes, which: …….. to an intercurrent disease, ☐Yes ☐No If yes, which: …… other, ☐Yes ☐No If yes, specify: ……

7. Device defect	☐Yes ☐ No
If yes, specify,	

Notifier	**Investigator**
Name and position: Signature	Name: Signature

Please send this form to:
Franck Pelletier
Head of Devices Vigilance
Fax: 03.20.14.40.13
E-mail: f.pelletier@cousin-biotech.com