Medtronic **Clinical Investigation Plan**	
Clinical Investigation Plan/Study Title	Xpede Clinical study
Study Product Name	Kyphon®Xpede™Bone Cement
Model/Specification	CX01A
Category of investigational medical device	Class III
Similar product in China	Yes
Class III medical devices requiring clinical trial approval:	No
Sponsor:	Medtronic SOFAMOR DANEK USA 1800 Pyramid Place, Memphis, TN USA 38132.
Local Sponsor	Medtronic (Shanghai) Management Co., Ltd. 11F, Building B, No 5, Lane 255, DongYu Road, Pudong, Shanghai
Document Version	Version 3 17 Sep 2018
Coordinating Investigator	Prof. Yang Huilin
Clinical trial institution	The First Affiliated Hospital of Soochow University 188 Shizi Street, Soochow, China

1. Investigator Statement and Institution Statement

Study Title	Xpede Study
Study product Name	Kyphon®Xpede™Bone Cement
Sponsor:	Medtronic SOFAMOR DANEK USA 1800 Pyramid Place, Memphis, TN USA 38132.
Local Sponsor	Medtronic (Shanghai) Management Co., Ltd. 11F, Building B, No 5, Lane 255, DongYu Road, Pudong, Shanghai
Clinical Investigation Plan Identifier	NA
Version Number/Date	Version 3 17 Sep 2018
1. I will conduct this clinical trial in strict compliance with the Declaration of Helsinki, current laws and regulations of China, and the requirements of the protocol; 2. And record all required data accurately on the Case Report Form (CRF) and complete the final report of the clinical trial on time; 3. The investigational medical device will be used only for this clinical trial and the receipt and use of the investigational medical device will be recorded completely and accurately and the records will be retained during the process of the clinical trial; 4. The monitor and verifier authorized or designated by the Sponsor and the regulatory authorities are allowed to conduct monitoring, verification and inspection for the clinical trial; 5.The clinical trial should be conducted in strict compliance with contract/articles of agreement signed by all parties. I have already read the clinical study protocol, including the above statement and I fully agree all the above requirements.	
Investigator's Signature:	
Investigator's Name:	
Date:	
Institution:	

Read and Approved by Clinical Research Institution

Study Title	Xpede Study
Study product Name	Kyphon®Xpede™Bone Cement
Sponsor:	Medtronic SOFAMOR DANEK USA 1800 Pyramid Place, Memphis, TN USA 38132.
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Version Number/Date	Version 3 17 Sep 2018

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Site Name

_____

Comments of Clinical Research Institution

_____

Signature/ Stamp

_____

Date (dd/mmm/yyyy)

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2. Glossary

Term	Definition
Adverse Event	Any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects, users or other persons , whether or not related to the investigational medical device. NOTE 1: This definition includes events related to the investigational medical device or the comparator. NOTE 2: This definition includes events related to the procedures involved. NOTE 3: For users or other persons, this definition is restricted to events related to investigational medical devices. (ISO 14155:2011 section 3.2) _____ The medical events with disadvantages occurred during the clinical study, no matter whether they are related to investigational medical devices or not. (CFDA Order No. 25 Article 93)
Adverse Device Effect (ADE)	Adverse event related to the use of an investigational medical device.

Term	Definition
	NOTE 1: This definition includes adverse events resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation, or any malfunction of the investigational medical device. NOTE 2: This definition includes any event resulting from use error or from intentional misuse of the investigational medical device. (ISO 14155:2011 section 3.1)
Audit	Systematic independent examination of activities and documents related to clinical investigation to determine whether these activities were conducted, and the data recorded, analyzed and accurately reported, according to the CIP, standard operating procedures, this International Standard and applicable regulatory requirements.
Case Report Forms (CRFs)	A paper or electronic data collection form, designed to collect information on each subject as required by the Study Protocol / Clinical Investigation Plan.
Charter	Document that describes the committee membership, roles and responsibilities, and processes to be utilized by the committee.
Clinical Data	Any data collected in a clinical study and stored in a study database or related database, including device databases and clinical study records (e.g., subject questionnaires, discharge summaries, save-to-disk and informed consent documents).
Clinical Database	The compilation of data fields that store the data collected for a study.
Clinical Investigation Plan (CIP)	Document that state(s) the rationale, objectives, design and proposed analysis, methodology, monitoring, conduct and record-keeping of the clinical investigation. Note: The term "protocol" is synonymous with "CIP". However, protocol has many different meanings, some not related to clinical investigation, and these can differ from country to country. Therefore, the term CIP is used in this International Standard.

Term	Definition
Clinical Study Report (CSR)	A written description of a study of any therapeutic, prophylactic, or diagnostic agent conducted in human subjects, in which the clinical and statistical description, presentations, and analyses are fully integrated into a single report.
Clinical Study Synopsis	An outline of the general requirements and parameters of the study. The synopsis is used as a tool in developing the protocol as well as providing insight as to what resources may be required to conduct the study.
Close-out Visit (COV)	A final monitoring visit to a site conducted to obtain all required study-related information, and to review ongoing and future study-related investigator responsibilities (e.g., regulatory inspector access, document archival, financial disclosure) per contractual agreements and relevant regulations.
Compliance (in relation to studies)	Adherence to all the study-related requirements, good clinical practice (GCP) requirements, and the applicable regulatory requirements.
Consent Form	See Informed Consent.
Ethics Committee (EC)	Independent body whose responsibility is to review clinical investigations in order to protect the rights, safety and well-being of human subjects participating in a clinical investigation. Also known as the Institutional Review Board (IRB). Note: For the purposes of this International Standard, "ethics committee" is synonymous with "research ethics committee," "independent ethics committee" or "institutional review board". The regulatory requirements pertaining to ethics committees or similar institutions vary by country or region.
Good Clinical Practice (GCP)	A standard for the design, conduct, performance, monitoring, auditing, recording, analyses, and reporting of clinical studies that provides assurance that the data and reported results are credible and accurate, and that the

Term	Definition
	rights, integrity, and confidentiality of study subjects are protected.
Inclusion/ Exclusion Criteria	The medical or social standards determining whether a person may or may not be allowed to enter a clinical study. These criteria are based on such factors as age, gender, the type and stage of a disease, previous treatment history, and other medical conditions. The criteria are not used to reject people personally, but to identify appropriate participants and keep them safe.
Independent	Not involved in the conduct of a clinical investigation, except for their specifically assigned responsibilities, in order to avoid bias or a conflict of interest.
Informed Consent	A process by which a subject voluntarily confirms his or her willingness to participate in a particular study, after having been informed of all aspects of the study that are relevant to the subject's decision to participate. Informed consent is documented by means of a written, signed and dated informed consent form.
Inspection	The act by a regulatory authority(ies) of conducting an official review of documents, facilities, records, and other resources that are deemed by the authority(ies) to be related to the clinical study and that may be located at the site of the study, at the sponsor's and/or contract research organization's (CROs) facilities, or at other establishments deemed appropriate by the regulatory authority(ies).
Institution	A person, other than an individual, who engages in the conduct of research on subjects or in the delivery of medical services to individuals as a primary activity or as an adjunct to providing residential or custodial care to humans. The term includes, for example, a hospital, retirement home, confinement facility, academic establishment, and device manufacturer.
Institutional Review Board (IRB)	Any board, committee, or other group formally designated by an institution to review, to approve the initiation of, and to conduct

Term	Definition
	periodic review of, biomedical research involving human subjects. The primary purpose of such review is to assure the protection of the rights and welfare of the human subjects. Also known as Ethics Committee (EC).
Interim Monitoring Visit (IMV)	A site visit conducted during the execution phase of a clinical study to assure the Investigator's obligations to the study protocol/CIP are being fulfilled and the facilities used in the clinical study continue to be acceptable.
Investigational Device	A device, including a transitional device, which is the object of an investigation.
Investigational Site	Institution or site where the clinical investigation is carried out.
Investigational Product	A product (e.g., Device, Drug, Software) that is being evaluated in a clinical study and; - is not approved/cleared, or - is different from the approved/cleared form, or - is being used for an unapproved or uncleared indication/use.
Investigator	A person responsible for the conduct of the clinical study at the study site. If a study is conducted by a team of individuals at a study site, the investigator is the responsible leader of the team and may be called the principal investigator. See also Sub-Investigator.
Investigator's Brochure (IB)	A compilation of the clinical and nonclinical data on the study product(s) that is relevant to the study of the study product(s) in human subjects.
Investigator Site File (ISF)	A study-specific file maintained by the Principal Clinical Investigator, which contains all documentation specific to their clinical site. Also called a Site Regulatory Binder.
Monitoring	Act of overseeing the progress of a clinical investigation and to ensure that it is conducted, recorded, and reported in accordance with the CIP, written procedures and the applicable regulatory requirements.

Term	Definition
Monitoring Visit	A visit to a clinical study site by a qualified monitor for the purpose of performing a site qualification visit (SQV), site initiation visit (SIV), interim monitoring visit (IMV) or close out visit (COV) activities.
Protocol	See Clinical Investigation Plan.
Protocol Amendment	A written description of a change(s) to or formal clarification of a protocol.
Publication	A medical or scientific written or electronic summary of research work that is used to educate external audiences, such as HCPs, on the use(s) or benefit(s) of Medtronic products and therapies.
Publication Plan	The specific tasks and deliverables in order to execute on the publications strategy.
Serious Adverse Device Effect (SADE)	Adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event.
Serious Adverse Event (SAE)	See definition in the Table 6 for SAE.
Site Initiation Visit (SIV)	A site visit designed to document general site readiness, including but not limited to, a review of study procedures and the Investigator's responsibilities with the investigator and site personnel.
Site Initiation	The process of gathering regulatory documents and conducting the activities required to activate a site to enroll subjects in a clinical study. The initiation process begins after the site is selected to participate in the clinical study.
Source Data	All information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical study necessary for the reconstruction and evaluation of the clinical study. Source data are contained in source documents (original records or certified copies).
Source Documents /Documentation	Original documents, data, and records (e.g., hospital records, clinical and office charts, laboratory notes, memoranda, subject's diaries

Term	Definition
	or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical study).
Sponsor	An individual, company, institution, or organization that takes responsibility for the initiation, management, and/or financing of a clinical study.
Study Deviation	An event where the clinical investigator or site personnel did not conduct protocol required procedures according to the study protocol.
Sub-Investigator (Sub-I)	Any individual member of the clinical study team designated and supervised by the investigator at a study site to perform critical study-related procedures and/or to make important study-related decisions (e.g., associates, residents, research fellows). See also Investigator.
Subject/Study Subject	An individual who participates in a clinical study either as a recipient of the study product(s) or as a control.
Suspension (study or site)	A temporary postponement of study activities related to enrollment and distribution of the product. (Possible for the total study or a single site.)
Termination (study or site)	Discontinuance, by sponsor or by withdrawal of EC or NMPA approval, of an investigation before completion.
Termination Letter	A letter terminating an agreement or contract.

3. Synopsis

Title	Xpede Study
Clinical Study Type	The Xpede Study is a prospective, 1: 1 randomized, single blind, multi-center human clinical trial.
Product Name	Kyphon®Xpede™ Bone Cement
Class of the product	III
Similar Product in China	Yes
Sponsor:	Medtronic SOFAMOR DANEK USA 1800 Pyramid Place, Memphis, TN USA 38132.
Local Sponsor	Medtronic (Shanghai) Management Co., Ltd. 11F, Building B, No 5, Lane 255, DongYu Road, Pudong, Shanghai Phone: +86 21 2032 5239
Indication under investigation	KYPHON™ Xpede™ Bone Cement is indicated for the treatment of pathological fractures of the vertebral body due to osteoporosis, cancer, or benign lesions using a cementoplasty (i.e. kyphoplasty or vertebroplasty) procedure. It is also indicated for the fixation of pathological fractures of the sacral vertebral body or ala using sacral vertebroplasty or sacroplasty. Cancer includes multiple myeloma and metastatic lesions, including those arising from breast or lung cancer, or lymphoma. Benign lesions include hemangioma and giant cell tumor. Pathological fracture may include a symptomatic microfracture (as documented by appropriate imaging and/or presence of a lytic lesion) without obvious loss of vertebral body height.
Investigation Contents	Medtronic (Shanghai) Management Co., Ltd is sponsoring the Xpede study for product registration in China. This study is a prospective, randomized, single-blinded, multi-site study conducted in mainland China. The study is considered an investigational trial in China. The purpose of the XPEDE study is to demonstrate that Kyphon® Xpede™ Bone Cement is non-inferior to the Mendec Spine Bone Cement in terms of safety and efficacy. A total of 180 patients will be enrolled over a period of 6 months and followed for 6 months after the procedure.
Product Status	Kyphon®Xpede™ Bone Cement: CE mark was obtained in May 2014; FDA approval was obtained in 2011. Investigational status in China
Primary Objective(s)	The primary objective is to demonstrate that: •the mean change of NRS score from baseline assessed at 6 months post operation in the subjects treated with Kyphon®Xpede™ Bone

	Cement is non-inferior to that in the subjects treated with Mendec Spine Bone Cement; •Change in Vertebral Body Angles from baseline at 6 months in the subjects treated with Kyphon®Xpede™ Bone Cement is non-inferior to that in the subjects treated with Mendec Spine Bone Cement
Secondary Objective(s)	Secondary objective is to evaluate the secondary endpoints including: Change of NRS score from baseline at 1 day and 3 months Change of ODI from baseline at 1 day, 3-month visit and 6-month visit. Change of SF-36 from baseline at 1 day, 3-month visit and 6-month visit Change in Vertebral body height restoration at 1 day and 3-month visit and 6 month Change in Vertebral Body Angles from baseline at 1 day, 3-month visit Adverse events through 6-month visit.
Study Design	This is a single blinded, randomized, multicenter study. Target population are patients who are diagnosed with pathological vertebral body fracture and will undergo BKP or VP procedures. 180 patients will be randomized to receive either Kyphon®Xpede™ Bone Cement or Mendec. Timeframe for patient visit includes V1 (pre-operative), V2 (operative), V3 (1d), V4 (3 months), V5 (6 months).
Randomization	180 patients will be randomized into 2 groups in a 1:1 ratio. Permuted block randomization stratified by site, the number of levels to be treated and the type of procedure (VP versus BKP) will be used.
Sample Size	180 patients will be enrolled and randomized
Inclusion/Exclusion Criteria	Subjects will be included if ALL of the following inclusion criteria are met: 1) Subject being diagnosed as having painful pathological vertebral body fracture, who is suitable for VP/BKP procedure (1-3 levels) according to clinic practice. 2) Subjects who are willing to participate in study through consent and willing to undergo study specific required procedures with expectancy of geographically stable for follow up duration. 3) Subjects are at least 18 and ≤80 years old . Subjects will be excluded if ANY of the following exclusion criteria is met: 1) Subject has a local or systemic infection 2) Subject has pains caused by other spine disease than painful pathological vertebral compression fracture 3) Subject has a medical condition with less than 1 year of life expectancy

	4) Subject is grossly obese, i.e. BMI⩾40 5) Subject has medical conditions that represent contraindications for the use of bone cement by investigator's decision 6) Subject has an allergy or an intolerance to bone cement component 7) Subject has past spinal surgeries at the target level(s) for which the VP/BKP procedure is suitable. 8) Subjects who are currently enrolled or planning to participate in a potentially confounding drug or device trial during the course of this study. Co-enrollment in concurrent trials is only allowed when document pre-approval is obtained from the Medtronic study manager and Medtronic Medical Advisor. 9) Pregnant women or breastfeeding women, or women of child bearing potential who are not on a reliable form of birth regulation method or abstinence. 10)Subjects with exclusion criteria required by local law (age or other). 11)Subjects with medical condition which precludes them from participation in the opinion of the Investigator
Study Procedures and Assessments	Data collection is performed at baseline (pre-operative – V1), during the procedure (V2), 1 day post-operative (V3),3 months (V4) and 6 months (V5) post procedure.
Safety Assessments	Adverse Events will be recorded and reported according to local regulatory requirements. It is the responsibility of the Investigator to abide by the adverse event reporting requirements stipulated by local law and the sites' Ethics Committee.
Statistics	This is a non-inferiority study. Since there are two primary efficacy endpoints, the overall sample size will be determined by the primary objective that requires the larger sample size. The non-inferiority hypothesis on the NRS requires 180 subjects (attrition: 15%) by 1:1 randomization schedule. Since the sample size on Angulation lead to 200 levels, and therefore to 148 subjects (attrition: 20%), the sample size will be 180 subjects. The study is considered as a success if both primary objectives are met. The data will be primarily analyzed according to the intention-to-treat principle and a Full Analysis Set will be used for primary final analysis. The analysis on the first primary endpoint based on NRS will use one measure per patient and the comparison will be between the average NRS in both groups. It will be claimed that XPEDE is not inferior to MENDEC with respect to NRS score if the upper bound of the two-

	sided 95% confidence interval of the difference ($\mu_X(t) - \mu_M(t)$) is less than the margin. The analysis on the second primary endpoint based on Index Vertebral Body Angles will use multiple data points per patient according to the number of levels treated. The analysis will be performed by means of Generalized Estimating Equation (or mixed models for repeated measures) using patient as the subject. The analyses based on freedom from event at 6 months will be described by means of Kaplan-Meier curves. Cox models will be fitted and hazard ratios (HRs) with 95% confidence intervals will be computed. The rate of event will be computed and reported separately for each group, together with their 95% confidence intervals. Rates were compared by means of either a mixed Poisson model or a negative binomial regression model (if over dispersion was present). Incident rate ratios (IRRs) and 95% confidence intervals were used to compare the two groups. Analysis of endpoints based on comparisons between groups on continuous measurements will be performed by Student's t-test or non-parametric test (Mann–Whitney U test) for normal and non-normal distributions, respectively. Categorical variable parameter comparisons will be performed using a Chi-square test, or a Mantel-Haenszel test for trend for ordinal variables with 3 or more categories.			
List of all clinical trial institutions and investigators for multicenter clinical trial	**Name of clinical trial institution**	**Investigator**	**Title**	**Contact information**
	The First Affiliated Hospital of Soochow University	Prof. Yang Huilin	Professor	188 Shizi Street, Soochow, China
	The First Affiliated Hospital of Zhengzhou University	Prof. Liu Hongjian	Professor	No. 1 East Jianshe Road, Zhengzhou
	Hunan Provincial	Prof. Liu Xiangyang	Professor	No. 61 West Jiefang Road, Changsha

	People's Hospital			

4. Introduction

4.1. Background

With the aging population, vertebral compression fracture (VCF) is nowadays representing a major issue in the health management of elderlies. VCFs can result as a consequence of osteoporosis but also malignant and benign tumors[1] . Percutaneous vertebroplasty (VP) and percutaneous balloon kyphoplasty (BKP) are two minimally invasive widely used vertebral augmentation procedures to stabilize vertebral body fractures and alleviate pain [2]. In both procedures, under fluoroscopy bone cement is injected into the vertebral body with a transpedicular approach.

During percutaneous vertebroplasty, a small needle is inserted percutaneous!y into the vertebral body through the pedicles. PMMA based bone cement is injected into the cancellous bone of the vertebral body. The bone cement fills the bony trabeculae to stabilize the bone.

During BKP, an Inflatable Bone Tamp (IBT) is inserted through the cannula into the vertebral body. Inflation of the IBT results in a restoration of vertebral body anatomy, with height restoration and angular deformity correction. IBT inflation is controlled by a pressure-measuring device; inflation of the IBT with radiopaque contrast material is visualized on intraoperative fluoroscopy. The IBT also compacts cancellous bone, which may help to provide stabilization. Void creation through cancellous bone compaction also reduces the potential for the fixation material to go beyond the region of its intended application. ' The IBT is removed, and the void created by the IBT is filled with viscous PMMA-based bone cement using a Bone Filler Device (BFD).

Polymethylmethacrylate (PMMA) has been used as biomaterial in orthopedic surgeries since the late 1960s. A large literature supports the use of bone cement as a bone void filler in patients with giant cell tumors. Other uses of PMMA bone cement include dental applications, contact and intraocular lenses, and filler material for bone cavities and skull defects.

Bone cements have a powder component and a liquid component that are mixed by the user just prior to delivery of the bone cement

[1] Yi Zhan, Jianzhong Jiang, Haifen Liao, Haitao Tan, Keqin Yang. Risk Factors for Cement Leakage After Vertebroplasty or Kyphoplasty: A Meta-Analysis of Published Evidence. World Neurosurgery [World Neurosurg] 2017 May; Vol. 101, pp. 633-642

[2] Wang H, Sribastav SS, Ye F, Yang C, Wang J, Liu H, Zheng Z. Comparison of Percutaneous Vertebroplasty and Balloon Kyphoplasty for the Treatment of Single Level Vertebral Compression Fractures: A Meta-analysis of the Literature. Pain Physician. 2015 May-Jun;18(3):209-22. Review

4.2. Purpose

Medtronic (Shanghai) Management Co., Ltd. is sponsoring the Xpede study in China. This study is a prospective, multi-site, randomized, single blinded, human clinical trial. The purpose of this clinical study is to confirm the efficacy and safety of the Kyphon®Xpede™ Bone Cement in human use in China. This study is expected to begin as a pre-market study using investigational product in China.

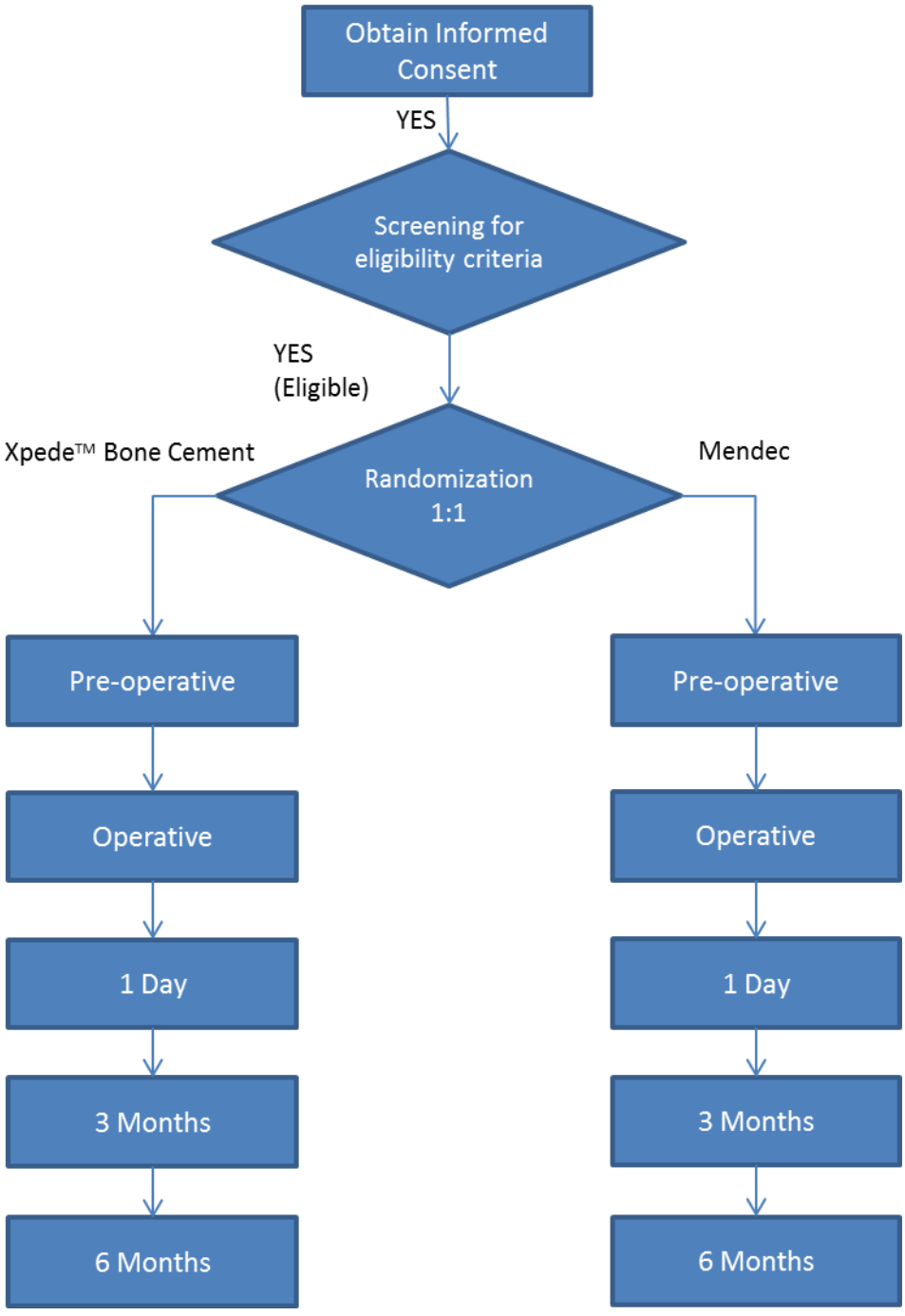


Figure 1: Study Flowchart

5. Objectives and Endpoints

5.1. Objectives

5.1.1. Primary Objective(s)

To demonstrate that Kyphon®Xpede™ Bone Cement is effective by showing that:

- the mean change of NRS score from baseline assessed at 6months post operation in the subjects treated with Kyphon®Xpede™ Bone Cement is non-inferior to that in the subjects treated with Mendec Spine Bone Cement;
- Change in Vertebral Body Angles from baseline at 6 months in the subjects treated with Kyphon®Xpede™ Bone Cement is non-inferior to that in the subjects treated with Mendec Spine Bone Cement.

5.1.2. Secondary Objective(s)

To evaluate the secondary endpoints defined in section 5.2.2

5.2. Endpoints

5.2.1. Primary Endpoint(s)

The primary endpoints are as follows:

- Change of NRS score at 6 months postoperative from baseline .
- Change of Index Vertebral Body Angles 6 months postoperative from baseline

5.2.2. Secondary Endpoints(s)

The secondary endpoints include:

- Change of NRS score from baseline at 1 day and 3 months
- Change of ODI from baseline at 1 day, 3-month visit and 6-month visit.
- Change of SF-36 from baseline at 1 day, 3-month visit and 6-month visit
- Change in Vertebral body height restoration at 1 day and 3-month visit and 6 month
- Change in Vertebral body Angles from baseline at 1 day, 3-month visit
- Adverse event through 6-month visit, in particular, the following events will be reported:

- Bone Cement Implantation Syndrome;
- Bone Cement leakage;
- Vertebral body compression fracture;
- Adjacent vertebral body fracture;

6. Study Design

The Xpede Study is a prospective, 1: 1 randomized, single blinded, multi-center human clinical trial designed to confirm the safety and efficacy profile of the Kyphon®Xpede™ Bone Cement for regulatory approval in China. This study will enroll up to 180 subjects in order to demonstrate that the Kyphon®Xpede™ Bone Cement is non-inferior to the Mendec Bone Cement by more than a small pre-specified amount in terms of the primary endpoint. This amount is defined as the non-inferiority margin (section 13 for details). Subjects will be randomly assigned with a 1:1 ratio to the Kyphon®Xpede™ Bone Cement arm or to the Mendec Bone Cement arm and then followed for a duration of 6 months in all sites. All study sites will be in China. All study sites and Investigators are provided under a separate cover.

6.1. Duration

It is expected to enroll 180 subjects in 3 sites in China. The estimated time of enrollment is anticipated to be approximately 6 months in total. Subjects will be followed during a period of 6 months after the study procedure so the estimated participation duration of each subjected is estimated to be 6 months. The total duration of the study is anticipated to be approximately 12 months.

Each study site is expected to enroll a minimum of 2 subjects during the study phase. In order to minimize potential bias associated with single center experience, a study site is limited to enroll no more than 90 (50%) of the total study enrollments (180). Each clinical trial institution, in principle, should launch and terminate clinical trials over the same period

6.2. Rationale

The goal of this study is to confirm the efficacy and safety of the Kyphon®Xpede™ Bone Cement. A prospective, randomized trial comparing the Kyphon®Xpede™ Bone Cement with a bone cement currently available in China with comparable characteristics and materials (Mendec Spine – Tecres, Verona, Italy) was designed to meet this objective

7. Product Description

7.1. General

Percutaneous vertebroplasty and kyphoplasty are minimally invasive techniques intended to be used for pathological fractures of the vertebral body. During this study either the Kyphon®Xpede™ Bone Cement or the currently available cement (Mendec Spine – Tecres, Verona, Italy) will be used. The Kyphon®Xpede™ Bone Cement is provided as a powder and a liquid which will need to be combined into a KYPHON™ Mixer. Following the KYPHON™ Mixer Instructions For Use, the powder and liquid components should be mixed for at least 30 seconds ensuring the ingredients are smoothly and uniformly combined. The liquid must moisten all the powder. When the bone cement is in a doughy state, it has reached the appropriate level of viscosity and is ready to be placed into the pathological fracture. The aim of the injection of bone cement is to stabilize the fractured vertebral body by filling the bony trabeculae.

Refer to Kyphon®Xpede™ Bone Cement additional details regarding directions for use, indications, contraindications, warnings and/or precautions. In this trial, the Kyphon®Xpede™ Bone Cement will not be tested for the fixation of pathological fractures of the sacral vertebral body or ala using sacral vertebroplasty or sacroplasty as stated in the most recent Instruction for use.

Mendec Spine is currently approved for the use in China and will be used according to its approved indications.

Table 1: Products information

Model Number	Component	Investigational or Commercially Available at Study Start
CX01A	Kyphon®Xpede™ Bone Cement	Investigational
13C2040	Mendec	Commercially available

Mendec will be used as comparator due to its similar characteristics as shown in **Table 2**

Table 2: Products Characteristics

	Mendec	Kyphon®Xpede™ Bone Cement
Power	**20g**	**20g**
Polymethlmethacrylate	**67.5%**	**69.1%**
Barium sulphate	**30%**	**30%**
Benzoly peroxide	**2.5%**	**0.9%**
Liquid	**9g**	**9.4 g**
Methylmethacrylate	**99.1%**	**99.4%**
N,N-dimethyl-p-toluidine	**0.9%**	**0.6%**
Hydroquinone	**75ppm**	**75ppm**

7.2. Manufacturer

Xpede™ Bone Cement : Medtronic SOFAMOR DANEK USA, INC. 1800 Pyramid Place, Memphis, TN USA 38132.

7.3. Packaging

Xpede™ Bone Cement will be labelled as per local regulations in China and products requiring investigational labelling will be labelled investigational as per local regulatory requirements.

7.4. Intended Population

KYPHON™ Xpede™ Bone Cement is indicated for the treatment of pathological fractures of the vertebral body due to osteoporosis, cancer, or benign lesions using a cementoplasty (i.e. kyphoplasty or vertebroplasty) procedure. It is also indicated for the fixation of pathological fractures of the sacral vertebral body or ala using sacral vertebroplasty or sacroplasty. Cancer includes multiple myeloma and metastatic lesions, including those arising from breast or lung cancer, or lymphoma. Benign lesions include hemangioma and giant cell tumor. Pathological fracture may include a symptomatic microfracture (as documented by appropriate imaging and/or presence of a lytic lesion) without obvious loss of vertebral body height.

7.5. Contraindications

PMMA bone cement is contraindicated in the presence of active or incompletely treated infection at the site where the bone cement is to be applied, for treatment of non-pathological, acute traumatic

fractures of the vertebra or sacrum, and in cases involving either displaced sacral fractures or compromise of the sacral foramina.

7.6. Product Use

The handling characteristics of bone cements are affected by operating room conditions, including the room temperature, temperature of the cement components prior to mixing, humidity, the geometry of the mixing apparatus, time spent mixing, and the geometry of the delivery device. Any change in one or more of these conditions can alter the handling characteristics of the bone cement, including the following:

- Handling period – the time it takes for the bone cement to reach the doughy state (the cement has reached the doughy state when it no longer sticks to surgical gloves).

- Working period – the time the bone cement remains in the doughy state, and can be delivered.

- Hardening period – the time it takes for the bone cement to harden or until it can no longer be delivered.

The user must be aware of these factors and adjust technique to account for variability in operating room conditions.

Under specific conditions in our laboratory using the KYPHON® Cement Delivery System, KYPHON® Xpede™ Bone Cement, had the following dough time, hardening time and working period, which allowed sufficient time for careful, minimally-invasive surgical introduction of the bone cement.

Table 3: Dough time, hardening time and working period informations

Average Room Temperature at Start of Mixing (±1°C)	***Average Dough Time (minutes)***	***Average Hardening Time (minutes)***	***Average Working Period (minutes)***
15	*12.8*	*42.8*	*30.0*
19	*5.8*	*21.9*	*16.1*
23	*2.4*	*15.8*	*13.4*
26	*2.0*	*13.3*	*11.3*

Lower temperatures or other changes in operating room conditions can increase the handling, working (doughy), and hardening periods. Conversely, higher temperatures or other changes in operating room conditions can decrease the handling, working (doughy), and hardening periods.

Table 4: Handling Characteristics of KYPHON® Xpede™ Bone Cement at 23 ± 1°C

Period	***Activity***	***Approximate Cumulative Time From Initiation of Mixing****
Mixing	*Mix liquid and powder*	*0-1 minutes*
Handling	*Transfer into delivery system*	*1-2 minutes*
Working (doughy state)	*Fill vertebral body*	*2-16 minutes*
Hardening	*Wait before completing procedure*	*16-20 minutes*

When the bone cement is in a doughy state, it has reached the appropriate level of viscosity and is ready to be placed into the pathological fracture. Do not insert the bone cement into the vertebral body until the bone cement has reached the doughy state.

Note: These cumulative time periods will vary depending on temperature and other factors. For example, the colder the environment, the longer the time necessary for the cement to develop the required doughy consistency. Warmer temperatures require more rapid preparation and handling. Ensure the cement's viscosity is high enough (doughy) before delivery begins. The doughy state is when the bone cement does not stick to surgical gloves.

* These times are based on cement prepared in Medtronic Spine LLC's laboratory. Times were obtained from bone cement mixed in a KYPHON® Mixer and delivered through the KYPHON® Cement Delivery System. Times may vary when other mixing methods, delivery devices and vacuum are used.

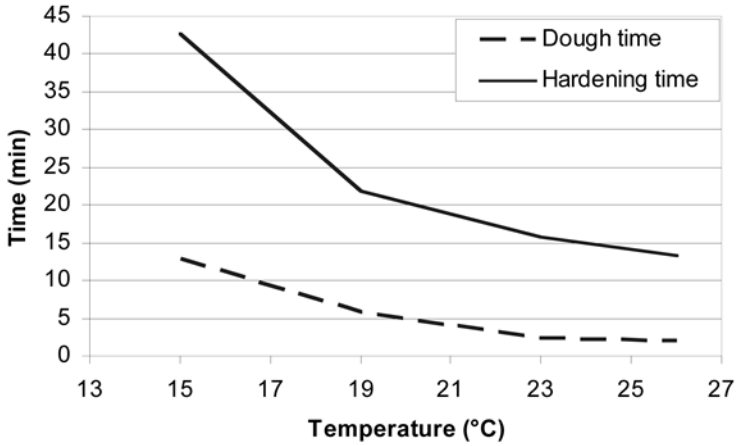


Figure 2: The effect of room temperature on the handling characteristics of KYPHON® Xpede™ Bone Cement is shown in the above time vs. temperature graph. At room temperatures of 15°C, 19°C, 23°C and 26°C, units of KYPHON® Xpede™ Bone Cement were mixed in a KYPHON® Mixer and transferred to KYPHON® Cement Delivery System. Dough time and hardening time were measured. The dashed line represents dough time (when dispensed cement no longer sticks to a surgical glove) and the solid line represents hardening time (when cement is too hard to dispense).

Preparation Procedures Per the note above, temperature can affect the handling of the cement. Prior to use, it is advised to keep the product at a temperature of 23 ± 1°C for a period of 24 hours. Prior to use, KYPHON® Xpede™ Bone Cement packaging should be examined for damage and the presence of all required components. Maintain aseptic transfer surgical technique to prevent possible infection. Maintain strict adherence to the instructions for mixing the powder and liquid to prevent possible dermatitis from the liquid monomer during handling. Assure that the inner package is undamaged, that the powder is not discolored (yellow or brown) and the liquid is not syrupy. These conditions indicate that the product has not been stored correctly. Assure that the preparation accessories are specifically compatible with the bone cement product. Do not open the vial of liquid over the mixing bowl to avoid the risk of glass fragments entering the dough.

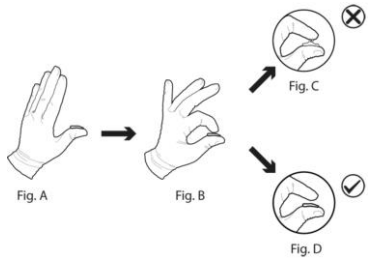
- Never add other substances or foreign bodies to the acrylic resin. Never modify the ratios between the liquid and solid components.
- Care should be taken in the mixing of the liquid and powder components such that the entire contents of the vial and packet are utilized. The liquid monomer and the powder component should be thoroughly mixed.

Mixing Procedure:

1. Always use sterile technique when mixing the bone cement.
2. Open powder packet and break open the vial. Immediately combine the powder and liquid into a KYPHON® Mixer.
3. Following the KYPHON® Mixer Instructions For Use, mix the powder and liquid components for at least 30 seconds ensuring the ingredients are smoothly and uniformly combined. The liquid must moisten all the powder.
4. After the powder and liquid have been thoroughly mixed, the transfer of the mixture into a cement delivery device(s) may begin.

Clinical Application Procedures:

When the bone cement is in a doughy state, it has reached the appropriate level of viscosity and is ready to be placed into the pathological fracture. Do not insert the bone cement into the vertebral body until the bone cement has reached the doughy state, as described below.



1. Dispense a fresh sample of about 2 cm of cement on to a surgically gloved finger (Fig. A).
2. Very gently touch the surface of the cement with a surgically gloved finger (Fig. B).
3. If the cement sticks to the glove and/or fibers (fine, hair-like threads) are observed to form between the fingers (Fig. C), then the cement has not yet reached the doughy state. In this case, repeat the previous steps at 30 second intervals.
4. When the gloved fingers separate cleanly with no fibers observed (Fig. D), the cement has reached the doughy state and is ready to be injected into the vertebral body.
5. Delivery of the bone cement into the vertebral body should begin in the anterior or central region of the vertebral body. Continue by allowing the bone cement to flow into the posterior area without moving the delivery device posteriorly. Care should be taken to avoid placing the delivery device against the anterior cortex.
6. While the bone cement hardens, it is important to maintain patient positioning until the end of the polymerization or hardening process.

The procedure may require technical support from Medtronic. The technical support is part of the standard of care to provide guidance on the appropriate use of the devices according to the IFU and Investigator Brochure. If support is present, it will be recorded on the Sponsor Technical Support List Product Training Requirements

The insertion of bone cement is part of routine BKP and VP procedure thus do not require any special training prior to the study. However, to ensure the quality of the study and minimize the investigator effect on study endpoints, prior to performing the procedure, it is important that surgeons read and understand the Instructions for Use that accompanies the Kyphon®Xpede™ Bone Cement.

Additionally, the selection of investigators should follow the criteria:

- All investigators should be trained by Medtronic on the appropriate use of Kyphon®Xpede™ Bone Cement.
- Investigator is qualified by training and expertise in the diagnosis and treatment of subjects requiring a BKP or VP procedures.
- investigator has associate senior professional title or qualification or above in the clinical trial institution (CFDA Order No. 25 Article 61)
- Investigator and clinical research staff have experience with conducting clinical device study that comply with applicable regulatory standards studies and have the time to conduct the study in accordance with the investigational plan.
- Agreement to comply with the investigational plan and applicable regulatory requirements.
- Adequate volume of potential subjects who meet the eligibility criteria
- Number of simultaneous competing clinical studies that might interfere with subject enrollment or study conduct.
- Appropriate facilities, resources, and equipment.
- Willing to undergo monitoring, auditing or inspection by Medtronic or relevant regulatory authorities.

7.7. Product Receipt and Tracking

Investigational product will be distributed to a site only when Medtronic has received all required documentation, has notified the site of site activation and the site has been authorized to enroll in the study. Distribution of the investigational product to study sites during the clinical study will be managed by Medtronic. The Investigator or site representative will verify that Investigational product supplies are received intact and in the correct amounts. This will be documented by signing and dating the Proof of Receipt or similar document.

Investigational products will be used only in the study according to the CIP.

7.8. Product Storage

KYPHON® Xpede™ Bone Cement should be stored in its original shipping materials. Proper care should be taken to ensure that KYPHON® Xpede™ Bone Cement will not be damaged. Store below 25°C and away from sunlight.

7.9. Product Return

The unused package of Xpede™ Bone Cement will be returned to Medtronic at end of every procedure. Please refer to your local Medtronic field personnel to arrange the return of the products.

7.10. Product Accountability

Device Disposition logs will be provided to the site and will be used for tracking of all investigational products.

These logs must be maintained at each investigational site to ensure traceability via assigned lot or serial numbers. It is the responsibility of the investigator to correctly handle, and track the investigational products. Disposition of investigational product will be reported when any of these investigational products are received, opened, implanted, disposed of or returned to Medtronic and completed in the related Investigational Products tracking documentation.

In addition, the used/residual/opened bone cement will be destroyed as medical waste on site according as to local procedures or regulations. All empty outer investigational product packaging will be inventoried by the site and verified by the site monitor. After investigational product accountability has been completed by the site monitor, empty packaging will be destroyed on site according to local procedures or regulations.

At the end of the procedure, the unused package of Xpede™ Bone Cement will be returned to Medtronic.

Mendec Bone cement will be distributed, handled, stored and returned according to each site standard procedure.

8. Selection of Subjects

8.1. Study Population

Up to 180 patients diagnosed with pathological vertebral body fracture and indicated for a BKP or VP procedure will be enrolled in up to 3 sites in China.

8.2. Subject Enrollment

Ethics Committee approval of the Xpede Study Clinical Investigation Plan and Informed Consent Form must be obtained prior to enrolling patients in the study.

Subjects are considered enrolled in the study upon signing the informed consent and meet all of the inclusion and none of the exclusion criteria. Informed consent must be obtained prior to performing any study-related procedures. Subjects will be assessed to ensure that they meet all of the inclusion and none of the exclusion criteria.

8.3. Inclusion Criteria

Subjects will be included if ALL of the following inclusion criteria are met:

1) Subject being diagnosed as having painful pathological vertebral body fracture, who is suitable for VP/BKP procedure (1-3 levels) according to clinic practice.

2) Subjects who are willing to participate in study through consent and willing to undergo study specific required procedures with expectancy of geographically stable for follow up duration.

3)) Subjects are at least 18 and ≤80 years old.

8.4. Exclusion Criteria

Subjects will be excluded if ANY of the following exclusion criteria is met:

1) Subject has a local or systemic infection

2) Subject has pains caused by other spine disease than pathological vertebral compression fracture

3) Subject has a medical condition with less than 1 year of life expectancy

4) Subject is grossly obese, i.e. BMI⩾40

5) Subject has medical conditions that represent contraindications for the use of bone cement by investigator's decision

6) Subject has an allergy or an intolerance to bone cement component

7) Subject has past spinal surgeries at the target level(s) for which the VP/BKP procedure is suitable.

8) Subjects who are currently enrolled or planning to participate in a potentially confounding drug or device trial during the course of this study. Co-enrollment in concurrent trials is only allowed when document pre-approval is obtained from the Medtronic study manager and Medtronic Medical Advisor.

9) Pregnant women or breastfeeding women, or women of child bearing potential and who are not on a reliable form of birth regulation method or abstinence.

10)Subjects with exclusion criteria required by local law (age or other).

11)Subjects with medical condition which precludes patient from participation in the opinion of the Investigator

9. Study Procedures

9.1. Schedule of Events

Table 5: Schedule of Events

Data to be collected	**Baseline & Randomization**	**Study Procedure (Day 0)**	**1 day Post Operative**	**3 months post op**	**6 months post op**	**Unscheduled**
Visit windows		Can be performed the same day of baseline	(After 24hours but not later than 1 week)	±2 weeks	±2 weeks	NA
Inclusion/Exclusion criteria	X					
Informed Consent Form[3]	X					
Demographics and medical history	X					

[3]To be obtained before any study related procedure

Physical examination	X					
MRI	X					
Study Procedure Data		X				
Concomitant specific medication	X		X	X	X	X
NRS score	X		X	X	X	X
ODI	X		X	X	X	X
AP/Lateral X-ray	X		X	X	X	X
SF36	X		X	X	X	X
Device disposition		X				
Adverse events review (subject and non-subject) and death information	Upon Occurrence					
Device Deficiency review	Upon Occurrence					
Protocol deviation review	Upon Occurrence					
Reason for premature study termination	Upon Occurrence					

9.2. Subject Consent

Informed consent is defined as legally effective, documented confirmation of a subject's (or their legally authorized representative or guardian) voluntary agreement to participate in the study. The Patient Informed Consent Form (ICF) is signed only after all relevant information regarding all aspects of the clinical study that are relevant to the subject's decision to participate throughout the clinical study have been provided to the subject. Subject consent will be obtained in accordance with local law and regulations. The ICF must be approved by the sponsor and the site's EC. The

documents referenced must be maintained in such a way as to assure control of the document (i.e. version and/or date) such that the version(s) approved by the EC are clear with a documented change history for all revisions. The principal investigator or his/her authorized designee will conduct the informed consent process. Refer to Appendix E: Informed Consent Templates.

The process for obtaining informed consent shall:

- Avoid any coercion of, or undue influence of subjects to participate
- Not waive or appear to waive subject's legal rights
- Provide documents to the subject in a language s/he is able to read and understand
- Use language that is non-technical and understandable to the subject or legal representative
- Provide ample time for the subject to consider participation
- Include a dated signature of the subject or legal representative acknowledging their participation in the study is voluntary. Include personally dated signatures of the principal investigator or an authorized designee responsible for conducting the informed consent process.
- The informed consent shall be documented before any procedure specific to the clinical investigation is applied to the subject.

In the event that the subject can't read or write, a witnessed (impartial third party) consent form and authorization/data protection will be allowed (as determine by local law), provided detailed documentation of the process is recorded in the subject's case history and the witness signs and dates the appropriate consent form and authorization.

The signed ICF and the authorization must be filed at the site. A copy of the ICF must be provided to the subject. The original signed ICF and the authorization or other privacy language where required by law must be retained and made available for review by site monitors, auditors, or inspectors.

The consent process should be documented at each site in source documents which may include Medical charts, progress notes of medical history sheets, etc. Any changes to a previously approved Informed Consent Form throughout the course of the study must be approved by Medtronic and then by the Ethics Committee reviewing the application before being used to consent a prospective study subject. The document(s) must be controlled (i.e. versioned and/or dated, per local law) to ensure it is clear which version(s) were approved by the Ethics Committee. All important new information should be provided to new and existing subjects throughout the study, and if relevant, all affected subjects shall be asked to confirm their continuing informed consent in writing.

9.3. Stratification and Treatment Assignment

Randomization will be performed according to a randomization schedule developed by the sponsor or sponsor's representative after the subject has signed the Informed Consent and prior to the surgical procedure. The clinical database will contain the randomization distribution system which will be used for this study.

Individuals who are randomized and receive the study treatment will be considered study (treated) subjects; only data from study (treated) subjects will be included in endpoint analysis.

Patients will be randomized 1:1 to either Xpede™ Bone Cement or Mendec bone cement. The sequence of treatments will be randomly permuted in blocks of 2 or 4 patients per block. The blocked randomization will be centralized and schedules will be created by the study statistician using statistical software. The randomization will be performed by the center via the EDC system (Oracle Clinic). To minimize the selection bias, the randomization procedure for this study will use the site (3 sites), the number of vertebral to be treated (1,2 or 3) and the type of procedure (2 procedure: VP and BKP) as stratification factors, so that there will be a separate permuted block randomization list for each stratum (18). This guarantees treatment balance within strata.

9.4. Baseline

Informed consent must be obtained prior to performing any study-specific procedure.

The following information will be collected at baseline:

• Demographic data

• Medical history,

• General physical examination

• MRI

• Imaging: A/P x ray imaging

• Concomitant medication

• All Adverse Events

• **Subject will complete:**
a.NRS
b.Quality of life questionnaires: SF-36 v2
c. Performance Status: Oswestry Disability Index (ODI) v2.1a:

Spinal disability will be assessed with the ODI questionnaire. The ODI is registered with the International Consortium for Health Outcome Measures as a standard outcome measure[4]. It is specific for spinal disorders and considered as the "gold standard" by several systematic reviews[5] [6] [7], and recent surgery guidelines[8] and has been used in several studies of spinal metastases[5].

9.5. Prior and Concomitant Medications

All medication therapy for optimal medical care will be given during the study period at the discretion of the physician(s). The specific concomitant medications listed below should be documented as concomitant medication.

• **Analgesic**(s) frequency and dose in past 24-hours will be recorded. All pain management (including but not limited to Nonsteroidal anti-inflammatory drugs (NSAIDs), acetaminophen, acetyl salicylic acid, tramadol, cannabinoids) will be collected. All opioid analgesics will be converted to oral morphine equivalent doses (OMED). Non-opioid analgesics will be counted as zero for OMED and will be analyzed separately.

• **Concurrent Osteoporosis medication**(s): Study subjects who have concurrent osteoporosis will be treated with antiresorptive therapy (e.g., bisphosphonates, parathyroid hormone (PTH),calcitonin), calcium and vitamin D as needed according to standard of care.

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9.6. Procedure day

The following information will be collected during the procedure:

[4] Fairbank JC. Why are there different versions of the Oswestry Disability Index? J Neurosurg Spine. 2014 Jan;20(1):83-6.
[5] Fairbank JC, Pynsent PB. The Oswestry Disability Index. Spine (Phila Pa 1976). 2000 Nov 15;25(22):2940-52; discussion 2952. Review
[6] Johnsen LG, Hellum C, Nygaard OP, Storheim K, Brox JI, Rossvoll I, Leivseth G, Grotle M. Comparison of the SF6D, the EQ5D, and the oswestry disability index in patients with chronic low back pain and degenerative disc disease. BMC Musculoskelet Disord. 2013 Apr 26;14:148.
[7] Gum JL, Glassman SD, Carreon LY. Clinically important deterioration in patients undergoing lumbar spine surgery: a choice of evaluation methods using the Oswestry Disability Index, 36-Item Short Form Health Survey, and pain scales: clinical article. J Neurosurg Spine. 2013 Nov;19(5):564-8
[8] Ghogawala Z, Resnick DK, Watters WC 3rd, Mummaneni PV, Dailey AT, Choudhri TF, Eck JC, Sharan A, Groff MW, Wang JC, Dhall SS, Kaiser MG. Guideline update for the performance of fusion procedures for degenerative disease of the lumbar spine. Part 2: assessment of functional outcome following lumbar fusion. J Neurosurg Spine. 2014 Jul;21(1):7-13

- Overall duration of the study procedure (skin to skin)
- Fluoroscopy duration
- Level(s) treated
- Type of anesthesia utilized
- Approach: unilateral versus bilateral BKP/VP
- BKP data including Balloon inflation volumes and pressures
- Kyphon® Xpede™ Bone Cement/Mendec volume
- Cement delivery system use
- All Adverse Events/Device Deficiencies
- Cement extravasation
- Inpatient versus outpatient status
- Length of stay

9.7. Follow up visits

Information collected post-treatment at 1 day and 3 and 6 months onsite follow-up visits for all subjects by the Investigator (or, if delegated, the Study Nurse/Coordinator) includes the following:

• Concomitant medications

• Re-intervention at initially treated level(s), if applicable

• Imaging: A/P x ray imaging will be collected at onsite follow-up visits

• All adverse events/device deficiencies

• Subject will complete:

a.NRS score

b.Quality of Life questionnaires: SF-36 v2

c. Performance Status: ODI v2.1a

9.8. Radiography assessment

Radiological measurements will be made both by the blinded site personnel and by a centralized, independent radiologist (corelab).

A. Vertebral Body Height

Vertebral body height should be assessed at Pre-Operative, 1 days, 3-, 6-month.

Vertebral Body Height in the lateral projection will be measured at each treated vertebra as well as the next adjacent vertebrae (superior and inferior) without fracture and reported in millimeters. Vertebral Body Height is the distance between comparable points on the superior and inferior

endplates of the vertebral body at the posterior (Hp), midline (Hm) and anterior (Ha) locations as shown in Figure 3.

Notes about Adjacent Vertebral Body Height Measurements:

Note 1: The normal estimated pre-fracture height of the treated vertebra will be based on the average of the nearest adjacent non-fractured vertebrae (see Figure 4 below). The reviewer will record the level of the nearest non-fractured level superior to and inferior to the treated level.

Note 2: When L5 is the treated vertebra, the estimated pre-fracture (predicted) height of L5 will be based on L4 or the nearest superior non-fractured level. The height of S1 is not suitable as a predictor of the pre-fracture height of L5.

Note 3: The height of the nearest adjacent, non-fractured, vertebrae may be calculated at a single time point and used for all measurements at other time points. In general, the adjacent level vertebral heights will be obtained at the Pre-Operative time point from standing neutral lateral x-rays.

Note 4: In some cases, the superior or inferior adjacent vertebra may be poorly visualized at the Pre-Operative visit due to inadequate image quality. In this situation, the adjacent vertebra may be excluded from the analysis, or a subsequent visit, e.g. Post-Operative, may be used to obtain a reliable measurement of the adjacent vertebral body height.

1) Posterior height (Hp) is obtained by placing a vertical line along the dorsal surface of the vertebral body from the posterior point of the superior vertebral body endplate to the posterior point of the inferior endplate.
2) Midline height (Hm) is obtained by placing a vertical line along the midline of the vertebral body from the midpoint of the superior vertebral body endplate to the midpoint of the inferior endplate. The height will be measured between the two opposing endplates. If the vertebra is tilted or image obliquely giving a double endplate appearance in the radiograph, the vertical midpoint of the intact endplate lines will be used as the reference point for measurement.
3) Anterior height (Ha) is obtained by placing a vertical line along the ventral surface of the vertebral body from the anterior point of the superior vertebral body endplate to the anterior point of the inferior endplate.

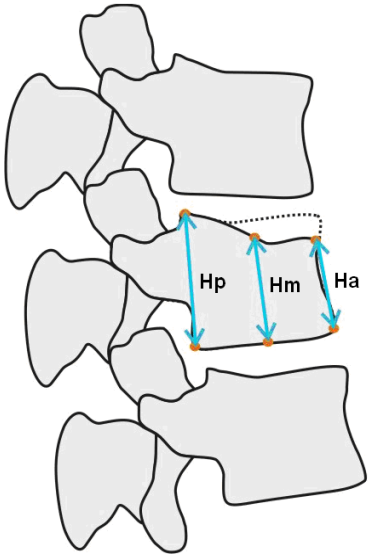

Figure 3: Vertebral Body Height

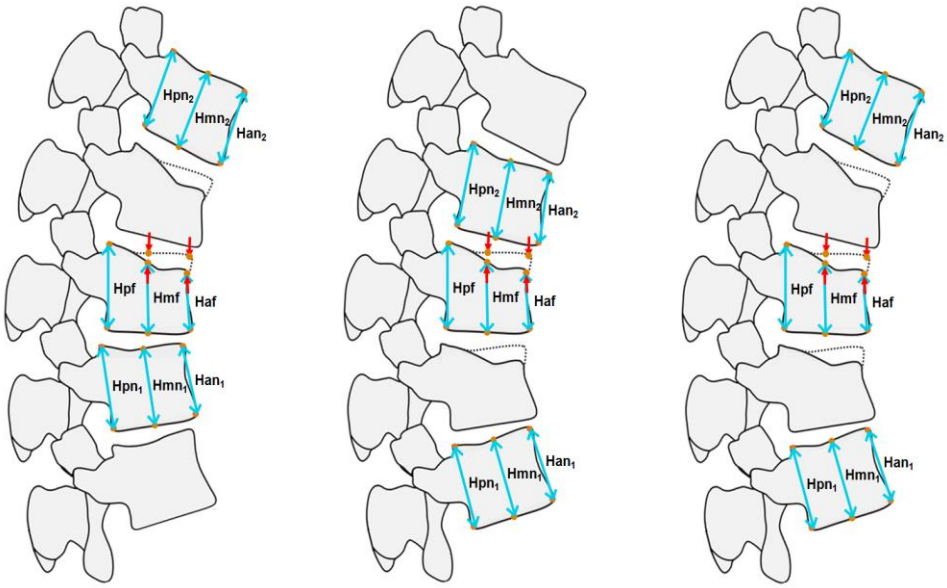

Figure 4: Examples of Using the Next Adjacent Non-Fractured Vertebra(e)

Magnification Adjustment

Vertebral Body Height will be adjusted for variation in image scale by the use of a magnification marker. The clinical sites are responsible for ensuring the use of magnification markers, provided by Medtronic, on all lateral images. Image readers will measure the diameter of the marker and the

ratio of the measurement diameter to the true diameter will define the magnification of the image. This magnification will be used to adjust all vertebral body height measurements to a common scale at each visit. If the marker is not present or not measurable at a particular visit, the reviewer may use a stable anatomical feature common with a calibrated visit to make a similar adjustment for scale differences.

B. Vertebral Body Angle

Vertebral body Angle should be assessed at Pre-Operative, 1 days, 3-, 6-month.

1) Two lines will be drawn, the first line along the superior endplate of the fractured vertebral body and the second line along the inferior endplate of the fractured vertebral body for each fractured vertebral body.
2) The angle between these two lines will then be measured. This is shown in Figure 5. Negative angles will be associated with a kyphosis (wedge-shaped) vertebral body; positive angles will be associated with lordotic (fish-mouthed) vertebral body. A zero-degree angle will indicate that the vertebral endplates are parallel.

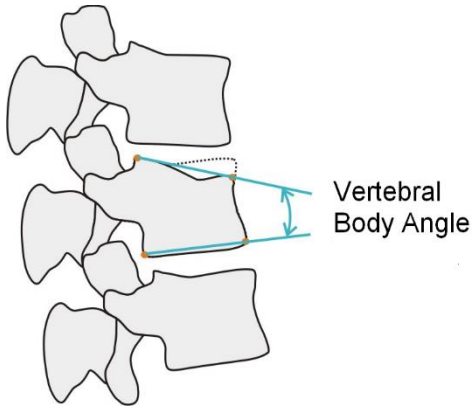

Figure 5: Example of Measuring Vertebral Body Angle of a Treated Vertebra Vertebral Body Angle of Index Fracture

9.9. Assessment of Efficacy

Efficacy will be evaluated by the blinded investigator or designed blinded site personnel status of primary endpoint and secondary endpoints related with efficacy.

X-ray images will be reviewed by an independent radiological reviewer (Corelab) who will be blinded to the subjects' treatment groups for each analysis.

Adjudications provided both by the site blinded personnel and by the Corelab will be analyzed separately and reported in the Clinical Study Report (CSR). Final conclusion will be made according to Corelab adjudication.

9.10. Assessment of Safety

Timely, accurate, and complete reporting and analysis of safety information is crucial for the protection of subjects, clinicians, and the sponsor. Reporting and analysis of safety data are mandated by regulatory authorities worldwide. Medtronic has established Standard Operating Procedures (SOPs) to ensure compliance with global regulatory safety reporting requirements. Study activities are conducted in accordance with these SOPs.

All adverse events are collected throughout the duration of this study, starting from the time of signing the ICF through study closure. Adverse Events are to be reported upon site awareness using an adverse event CRF, capturing date of the event; date site became aware of the event, diagnosis of the event, actions taken, assessment of seriousness, relatedness and outcome.

Unavoidable Adverse Events (refer to Table 7) need not be reported unless the adverse event worsens or is present outside the stated timeframe.

Adverse Events will be recorded and reported according to local regulatory requirements and are outlined in Table 8. It is the responsibility of the Investigator to abide by the adverse event reporting requirements stipulated by local law and the sites' Ethics Committee.

9.11. Recording Data

Clinical data will be collected at baseline, operative day, 1 day post-operative, 3-month and 6-month post-operative visits. Data will be collected using electronic case report forms (eCRFs) using an electronic data management system for clinical studies. Data will be stored in a secure, password-protected database, which will be backed up nightly. Data will be reviewed using programmed and manual data checks. Data queries will be made available to study sites for resolution. At the end of the study, the data will be frozen and retained indefinitely by Medtronic.

Medtronic will oversee all data management functions and provide support if necessary. Leading site will be accountable for data management and analysis about the study data in a centralized manner according to local regulations.

9.12. Deviation Handling

A deviation is defined as an event within a study that did not occur according to the CIP or the Clinical Trial Agreement. Prior approval by Medtronic is expected in situations where the investigator anticipates, contemplates, or makes a conscious decision to deviate. Prior approval is not required when a deviation is necessary to protect the life or physical well-being of a subject in an emergency or in unforeseen situations beyond the investigator's control (e.g., subject failure to attend scheduled follow-up visits, inadvertent loss of data due to computer malfunction or inability to perform required procedures due to subject illness).

All study deviations must be reported on the Case Report Form regardless of whether medically justifiable, pre-approved by Medtronic, an inadvertent occurrence, or taken to protect the subject in an emergency. The description of the deviation and justification must be documented.

Once a deviation has been identified it should be reported to Medtronic as soon as possible. Deviations may be identified through numerous sources, including but not limited to: telephone conversations, site monitoring, subject record, or data review.

It is the site's responsibility to report deviations in compliance with their EC/IRB policies and/or local laws.

For medically justifiable conditions which preempt a subject's ability to complete a study-required procedure, it may be permitted to complete only one deviation which will apply to all visits going forward. This may also apply for other unforeseen situations (e.g., the subject permanently refuses to complete a study required procedure and the data will not contribute to the primary end point analysis). However, prior approval from Medtronic is required for such situations.

In the occurrence of a corrupted device interrogation file, Medtronic may request a deviation to document that a readable interrogation file is unavailable. Deviations for missing device interrogation file(s) and missing or incomplete electrical testing at the same visit may be reported on one deviation CRF.

In the event the deviation involves a failure to obtain a subject's informed consent, or is made to protect the life or physical well-being of a subject in an emergency, the deviation must be reported to the IRB and Medtronic within five (5) working days. Reporting of all other study deviations should comply with IRB policies and/or local laws and must be reported to Medtronic as soon as possible upon the site becoming aware of the deviation. Reporting of deviations must comply with EC policies, local laws, and/or regulatory requirements.

Medtronic is responsible for analyzing deviations, assessing their significance, and identifying any additional corrective and/or preventive actions (e.g., amend the CIP, conduct additional training, and terminate the investigation). Repetitive or serious investigator compliance issues may represent a

need to initiate a corrective action plan with the investigator and site, and in some cases, necessitate suspending enrollment until the problem is resolved or ultimately terminating the investigator's participation in the study.

9.13. Subject Withdrawal or Discontinuation

Every attempt should be made to follow all treated subjects through study closure.

Upon exiting from the study, no further study data will be collected or study visits will occur for the subject. No study specific medical care will be provided for subjects after the study has been completed and subject will be treated according to the standard routine practice after the study period.

All data available through the time of the subject's exit will be used for analysis. In the event of study exit, the investigator should discuss with the subject the plans for future care and treatment. The investigator should explain that the subject will continue to receive standard medical care. Alternative treatment, such as medication options, or follow-up through standard of care procedures instead of study procedures, and medical consequences should also be discussed. The investigator must notify the subject of any significant new findings that may become available during the course of the study, which are pertinent to the safety and well-being of the subject.

Exit

Subjects may be exited from the study for any of the following situations:

- Subject does not meet inclusion/exclusion criteria and has not been treated
- No BKP or VP attempted
- Procedure attempted but no bone cement was injected
- Subject chooses to withdraw from the study
- Investigator deems withdrawal necessary (medically justified or inclusion/exclusion criteria not met, failure of subject to maintain adequate study compliance)

In the event that a subject is exited from the study prior to study closure, all efforts should be made to continue following the subject until all unresolved procedure or product related adverse events are resolved or they are ongoing and no further actions will be taken.

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Lost to Follow-up

In the case that the subject is determined to be lost to follow-up, details of a minimum of three attempts and the method of attempt (e.g., one letter and two phone records or two letters and one phone record) to contact the subject must be recorded. In addition, the requirements set by the governing EC/IRB for subjects lost to follow-up must be followed.

10. Risks and Benefits

10.1. Potential Risks

Medtronic follows rigorous Quality Assurance and Control procedures throughout the life of a product, from the business analysis phase through development, market release, and post-market surveillance.

VP and BKP are not investigational procedures and the risk associated with VP or BKP procedures are the same as for the one performed per clinical practice.

VP And BKP are the two procedures that will be used in both the investigational group (Xpede group) and the control group (Mendec) and the randomization will be stratified by the procedures. Hence the focus of risk and benefit analysis should be purely on the usage of Xpede versus Mendec

Serious adverse events, some with fatal outcome, associated with the use of acrylic bone cements as specified in the IFU include:

- cardiac arrest
- cerebrovascular accident
- myocardial infarction
- pulmonary embolism

Other reported adverse events relevant to the anatomy being treated with acrylic bone cements include:

- deep or superficial wound infection
- fistula
- hematoma
- hemorrhage
- heterotopic new bone formation
- extravasation of bone cement potentially resulting in but not limited to:
- compression or irritation of nerve structures, such as the spinal cord or nerve roots, causing radiculopathy, parasthesia, paraplegia or paralysis and/or;
- introduction into the vascular system resulting in embolism of the lung and/or heart or other

clinical sequelae

- pyrexia due to allergy to bone cement
- short-term conduction irregularities
- thrombophlebitis
- transitory fall in blood pressure
- migration of hardened bone cement bolus

10.2. Potential Benefits

The potential benefits of the KYPHON® Xpede™ Bone Cement are consistent with the vertebral body fracture therapy provided by similar currently approved Bone Cement.

Possible benefits of the use of bone cement include vertebral body height restoration, angular deformity correction, vertebral body volume increase, reduction in back pain, reduction in the number of days per month that the subject remains in bed, improvement in quality of life, improvement in ability to perform activities of daily living, subject satisfaction with the procedure, improvement in pain and mobility.

The information gained from this study could result in the improved management of patients suffering from Vertebral body fracture. Additionally, information collected from this study may assist in the design of new product(s)/therapy(ies) and/or instructions for use.

10.3. Risk-Benefit Rationale

KYPHON® Xpede™ Bone Cement had already been approved and widely used in different regions around the world, including EU and USA.

Risks associated with using the KYPHON® Xpede™ Bone Cement are similar to those associated with any other approved bone cement used during VP, BKP procedures.

For control arm Mendec Spine, it is a NMPA approved product. So the risks are also similar to using any other approved Bone Cement.

Compared with eligible patients who receive routine hospital care (any approved DES) and do not participate in this study, subjects will have very limited extra risks than using any approved DES.

Based on post market risk analysis and on the published scientific literature on equivalent products that are currently on the market and indicated for the same intended use as the KYPHON® Xpede™

Bone Cement, we anticipate that the benefits of using the KYPHON® Xpede™ Bone Cement outweigh the risks associated with the use of this product.

10.4. Probability analysis of success

The manufacturing system of Medtronic has been tested and proven for many years. The quality of the investigational device has been carefully examined and verified before delivery. The investigational device has been commercially available globally, including the Europe and many other countries. The basic principles, structure composition and materials etc. either comply with the international and domestic standards, or have been carefully examined and verified by Medtronic, as well as tested, qualified by NMPA certificated medical device testing organization. The study design of this study complies with related NMPA instructions and requirements of ethical review, and all potential subjects will be strictly selected according to indications of the investigational device.

10.5. Probability analysis of failure

Although regulatory, ethical, scientific and medical requirements have been fully taken into consideration, the unanticipated risk in the clinical application of investigational device could lead to failure of this study. Potential risks could be reduced with well-trained study staff and strict protocol compliance.

11. Adverse Events and Device Deficiencies

11.1. Definitions/Classifications

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Table 6: Adverse Event Definitions

Event Type	Definition
Adverse Event (AE)	Any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects, users or other persons, whether or not related to the investigational medical device. *NOTE 1: This definition includes events related to the investigational medical device or the comparator.* *NOTE 2: This definition includes events related to the procedures involved.* *NOTE 3: For users or other persons, this definition is restricted to events related to investigational medical devices.*

Event Type	Definition
	(ISO 14155:2011[9] section 3.2)
	The medical events with disadvantages occurred during the clinical study, no matter whether they are related to investigational medical devices or not. *(CFDA Order No. 25 Article 93)*
Serious Adverse Event (SAE)	Adverse event that a) led to death, b) led to serious deterioration in the health of the subject, that either resulted in 1) a life-threatening illness or injury, or 2) a permanent impairment of a body structure or a body function, or 3) in-patient or prolonged hospitalization, or 4) medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function, c) led to fetal distress, fetal death or a congenital abnormality or birth defect. *NOTE: Planned hospitalization for a pre-existing condition, or a procedure required by the CIP, without serious deterioration in health, is not considered a serious adverse event.* *(ISO 14155:2011 section 3.37)*
	Any untoward medical occurrence during the clinical study: results in death or serious deterioration in health; life-threatening diseases or injuries; causing permanent damage to the body structure or function; requires hospitalization or prolongation of hospitalization; requires medical operations or intervention for preventing from persistent or significant disability/incapacity; results in fetal distress, fetal death, or congenital anomaly/birth defect. *(CFDA Order No. 25 Article 93)*
Adverse Device Effect (ADE)	Adverse event related to the use of an investigational medical device. *NOTE 1: This definition includes adverse events resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation, or any malfunction of the investigational medical device.* *NOTE 2: This definition includes any event resulting from use error or from intentional misuse of the investigational medical device.* *(ISO 14155:2011 section 3.1)*
Serious Adverse Device Effect (SADE)	Adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event. *(ISO 14155:2011 section 3.36)*

[9] International Standard ISO 14155:2011(E). Clinical investigation of medical devices for human subjects – Good Clinical Practice.

Event Type	Definition
Unanticipated Serious Adverse Device Effect (USADE)	Serious adverse device effect which by its nature, incidence, severity or outcome has not been identified in the current version of the risk analysis report. *NOTE: Anticipated serious adverse device effect (ASADE) is an effect, which by its nature, incidence, severity or outcome has been identified in the risk analysis report.* *(ISO 14155:2011 section 3.42)*
Device Deficiency(DD)	Inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety or performance. *NOTE: Device deficiencies include malfunctions, use errors, and inadequate labeling.* *(ISO 14155:2011 section 3.15)*
	Any unreasonable risk caused by a medical device in normal use during clinical study that may endanger human health or life safety, such as label error, quality issues, malfunction and etc. *(CFDA Order No. 25 Article 93)*

Adverse Event Relationship Classification

Causality assessments define the relationship between the use of the medical device (including the medical-surgical procedure) and the occurrence of each adverse event. During causality assessment activity, clinical judgment shall be used and the relevant documents, such as the Clinical Evaluation Report and the Risk Management Report shall be consulted, as all the foreseeable serious adverse events and the potential risks are listed and assessed there. The presence of confounding factors, such as concomitant medication/treatment, the natural history of the underlying disease, other concurrent illness or risk factors shall also be considered.

The sponsor and the investigators will use the following definitions to assess the relationship of the adverse event to the investigational medical device (or comparator) or procedures.
1) Not related: relationship to the device or procedures can be excluded when:

- the event is not a known side effect of the product category the device belongs to or of similar devices and procedures;

- the event has no temporal relationship with the use of the investigational device or the procedures;

- the event does not follow a known response pattern to the medical device (if the response pattern is previously known) and is biologically implausible;

- the discontinuation of medical device application or the reduction of the level of activation/exposure - when clinically feasible - and reintroduction of its use (or increase of the level of activation/exposure), do not impact on the serious event;

- the event involves a body-site or an organ not expected to be affected by the device or procedure;

- the event can be attributed to another cause (e.g. an underlying or concurrent illness/ clinical condition, an effect of another device, drug, treatment or other risk factors);

- the event does not depend on a false result given by the investigational device used for diagnosis, when applicable;

- harms to the subject are not clearly due to use error;

- In order to establish the non-relatedness, not all the criteria listed above might be met at the same time, depending on the type of device/procedures and the event.

2) Unlikely: the relationship with the use of the device seems not relevant and/or the event can be reasonably explained by another cause, but additional information may be obtained.

3) Possible: the relationship with the use of the investigational device is weak but cannot be ruled out completely. Alternative causes are also possible (e.g. an underlying or concurrent illness/ clinical condition or/and an effect of another device, drug or treatment). Cases were relatedness cannot be assessed or no information has been obtained should also be classified as possible.

4) Probable: the relationship with the use of the investigational device seems relevant and/or the event cannot reasonably be explained by another cause, but additional information may be obtained.

5) Causal relationship: the serious event is associated with the investigational device or with procedures beyond reasonable doubt when:

- the event is a known side effect of the product category the device belongs to or of similar devices and procedures;

- the event has a temporal relationship with investigational device use/application or procedures;

- the event involves a body-site or organ that
    - o the investigational device or procedures are applied to;
    - o the investigational device or procedures have an effect on;
- the serious event follows a known response pattern to the medical device (if the response pattern is previously known);

- the discontinuation of medical device application (or reduction of the level of activation/exposure) and reintroduction of its use (or increase of the level of activation/exposure), impact on the serious event (when clinically feasible);

- other possible causes (e.g. an underlying or concurrent illness/ clinical condition or/and an effect of another device, drug or treatment) have been adequately ruled out;

- harm to the subject is due to error in use;

- the event depends on a false result given by the investigational device used for diagnosis, when applicable;

- In order to establish the relatedness, not all the criteria listed above might be met at the same time, depending on the type of device/procedures and the event.

The sponsor and the investigators will distinguish between the adverse events related to the device and those related to the procedures (any procedure specific to the clinical investigation). An adverse event can be related both to procedures and the device. Complications of procedures are considered not related if the said procedures would have been applied to the patients also in the absence of device use/application.

In some particular cases the event may be not adequately assessed because information is insufficient or contradictory and/or the data cannot be verified or supplemented. The sponsor and the Investigators will make the maximum effort to define and categorize the event and avoid these situations. Where the sponsor remains uncertain about classifying the event, it should not exclude the relatedness and classify the event as "possible".

Unavoidable Adverse Event Related to the Procedure: An Adverse Event inherent to a surgical procedure that is expected to occur in all subjects for a projected duration including but not limited to the one listed in Table 7.

Table 7: Unavoidable Adverse Events

Event Description	Time Frame (hrs) from end of Procedure
Anesthesia related nausea / vomiting	24 hrs
Low-grade fever (<100°F or < 37.8°C)	48 hrs
Mild to moderate bruising / ecchymosis	168 hrs (7 days)
Sleep problems (insomnia)	72 hrs

Unavoidable events shall not be reported as AE unless the adverse event worsens or is present outside the stated timeframe.

11.1.1. Subject Death

All subject deaths must be reported by the investigator to Medtronic as soon as possible after the investigator first learns of the death. Document the adverse event that led to the subject death on an Adverse Event form. Further supporting evidence that is not originally provided by the site may be requested by Medtronic to aid in the adjudication of the death.

A copy of the death certificate, if available and allowed by state/local law, should be sent to the Medtronic. When a death occurs in a hospital, a copy of the death summary report and all relevant hospital records should be sent to the Medtronic, if available. If an autopsy is conducted, the autopsy report should also be sent to the Medtronic if available and allowed by state/local law. When the death occurs at a remote site, it is the investigative site's responsibility to attempt retrieval of information about the death. In summary, the following data will be collected:

- Date of death
- Detailed description of death
- Cause of death
- Relatedness to system and/or procedure
- Death summary/hospital records (if available and allowed by local law)
- Autopsy report (if available and allowed by local law)
- Death certificate (if available and/or allowed by local law)

11.2. Reporting of Adverse Events and Device deficiencies

Adverse Events will be recorded and reported according to local regulatory requirements and are outlined in Table 8. It is the responsibility of the Investigator to abide by the adverse event reporting requirements stipulated by local law and the sites' Ethics Committee. Investigators are required to evaluate and document all AEs and Device Deficiencies (per the definitions in Table 6) observed in study subjects from the time they enrolled (signed the ICF) until they are no longer participating in the study. AEs and Device Deficiencies should be collected for both the study device as well as for the comparator. AEs should be followed until one of these criteria is met:

- Until the AE resolves
- Until no further action can be taken for an ongoing AE
- Until the subject exits the trial, or
- Until trial closure

NOTE: In the case of permanent impairment, continue to follow the event until it stabilizes and the overall clinical outcome has been ascertained.

The investigator is not required to classify USADE.

11.3. Emergency contact details

For emergency contact regarding a SAE and/or SADE, investigators should contact their Medtronic clinical study representative or monitor immediately (refer to the study contact list provided in the site's study documents binder/investigator site file or refer to the contact information provided on the title page). A list of contact information will be kept separately.

AE Reporting Requirements

Table 8: AE reporting Requirements

For the following events, reporting requirements are: • **Serious Adverse Events (SAE)**	
Investigators shall immediately adopt appropriate therapeutic measures for subjects, and simultaneously report to the management department of medical device clinical study in clinical Research institutions in written form. Management department of medical device clinical study shall report to:	
Medtronic	Immediately
Local food and drug regulatory authority and health and family planning regulatory authority of the province, autonomous region and municipality directly under the central government where the clinical Research institution locates	Within 24 hours
Ethics Committee	Within 24 hours/per EC's requirements
For the following events, reporting requirements are: • **All other AEs** • **All other Device Deficiencies**	
Investigators shall record all the adverse events and device deficiencies occurred during the clinical study. Investigators shall analyze the reasons for the events with Medtronic and document the analysis result in written report, including the comments of continuing. Suspending or terminating study, which shall be reported to the Ethics Committee through management department of medical device clinical study in clinical Research institutions for review.	
To Medtronic	Submit in a timely manner after the investigator first learns of the event.
To Ethics Committee	Per EC's requirements
For the following events, reporting requirements are: • **Serious Adverse Events (SAE)** • **DD with SAE potential**	
Medtronic submits to:	
The food and drug regulatory authorities and health and family planning competent authorities at the same level	Within 5 working days upon being informed
Other clinical Research institutions and investigators participating in the study	As per local reporting requirement

Ethics Committee	Timely report to EC of the clinical Research institution through management department of medical device clinical study

12. Statistical Design and Methods

Osteoporotic vertebral compression fractures (OVCFs) have gradually evolved into a serious health care problem globally. In order to reduce the morbidity of OVCF patients and improve their life quality, two minimally invasive surgery procedures, vertebroplasty (VP) and balloon kyphoplasty (BKP), have been developed. Both VP and BKP require the injection of bone cement into the vertebrae of patients to stabilize fractured vertebra. As such, bone cement as the filling material plays an essential role in the effectiveness of these treatments. The study will randomize subjects into two arms the Xpede and the Mendec as comparative products. The Mendec Bone Cement has been launched on China Market and has very similar composition material with the Kyphon®Xpede ™ Bone Cement and they are both polymethylmetacrylate (PMMA).

Due to these reasons the design of this study is a non-inferiority based on the margin δ as the maximum acceptable extent of clinical non-inferiority of Kyphon®Xpede™ Bone Cement.

Since there are two primary efficacy endpoints, the overall sample size will be determined by the primary objective that requires the larger sample size. The non-inferiority hypothesis on the NRS requires 154 subjects and including 15% of potential loss-to-follow-up, the total sample size for the study will be 178 randomized subjects by 1:1 randomization schedule. If we use 3 * 3 * 2 strata, the sample size should be 180 to be divisible of 18. Considering an average of 1.35 level per patient (FREE trial 72% with 1 level, 21% with 2 levels, 7% with 3 levels[10]), we should have around 243 levels treated on 180 patients. Since the sample size on Angulation lead to 200 levels, and therefore to 162 subjects, the sample size will be 180 subjects. The study is considered as a success if both primary objectives are met.

[10] Jan Van Meirhaeghe, Leonard Bastian, Steven Boonen, Jonas Ranstam, John B. Tillman, Douglas Wardlaw, on behalf of the FREE investigators. A Randomized Trial of Balloon Kyphoplasty and Nonsurgical Management for Treating Acute Vertebral Compression Fractures. SPINE Volume 38, Number 12, pp 971–983

13. Sample size determination

13.1. Primary Objective #1 (Efficacy)

The first primary objective of this study is to demonstrate that the efficacy of Xpede™ Bone cement (Experimental group) is not inferior to the MENDEC (Control group) in terms of NRS score improvement at 6 months (24 weeks) postoperative from baseline.

13.1.1. Background

Considering that the VAS and the NRS are reproducible and comparable methods for measuring pain, the literature search was performed on the VAS. From a Systematic Review aimed to update the evidence base for Balloon Kyphoplasty (BKP) and Vertebroplasty (PV) in the management on patients with VCFs, the mean preoperative and postoperative VAS scores (standard deviations) were 8.36 (0.78) and 2.68 (1.09), respectively[11]. In a population of osteoporotic fractures or vertebral metastasis after vertebroplasty the VAS mean (standard deviation) scores were 7.8 (1.2) before the procedure and 3.5 (1.3) at 6 months follow-up[12]. Another paper based on the assessment of the treatment of spinal metastases, the pre-operative VAS mean (standard deviation) score was 6.85 (0.97), which decreased to 6 months 3.58 (1.63)[13]. From the KAVIAR study[14] the estimated standard deviation for NRS is 3.27 (at 3 and 12 months visit).

13.1.2. Sample Size Calculations

Sample size calculations were performed in SAS software (SAS Institute Inc., Cary, NC, USA). A sample size is determined such that the non-inferiority of the primary objective is demonstrated that results are not appreciably worse in XPEDE arm compared to MENDEC Spine arm. Based on this information the assumptions for the sample size are:

[11] Gemma Marcucci, Maria Luisa Brandi. Kyphoplasty and vertebroplasty in the management of osteoporosis with subsequent vertebral compression fractures. Clinical Cases in Mineral and Bone Metabolism 2010; 7(1): 51-60

[12] Maiettini D., Orgera G., Bisaccia M., Piscitelli L., Laurino F., Meccariello L., Rebonato S., Schiaroli E., Rossi M. and Rebonato A.. Percutaneous Vertebroplasty Improves Pain Control and Quality of Life in Patients Suffering from Back Pain: A Single Center Experience.

[13] Feng C., Yong-Hui X., Wen-Zhen C., Wei S., Yang G., Bo F. and Difei W. Percutaneous kyphoplasty for the treatment of spinal metastases. ONCOLOGY LETTERS 11: 1799-1806, 2016

[14] Dohm M, Black CM, Dacre A, Tillman JB, Fueredi G; KAVIAR investigators. A randomized trial comparing balloon kyphoplasty and vertebroplasty for vertebral compression fractures due to osteoporosis. AJNR Am J Neuroradiol. 2014 Dec;35(12):2227-36.

- The NRS score which ranges from 0 to 10 is assumed to be approximately normally distributed.
- The NRS score is to be assessed at 24 weeks (6 months) after the procedure.
- The NRS at 24 weeks (6 months) is expected to be 3.5 in the MENDEC Spine treatment, and 3.5 or more in the Xpede. A difference in NRS score of 1.5 or less is considered clinically unimportant for this comparison[15]. It is considered the maximum acceptable increase in NRS score compared to the MENDEC Spine arm.
- The standard deviation of the NRS score is expected to be approximately 3.27 (the highest value from the literatures sited above) for each treatment. Common standard deviation will be assumed for both arms.
- The sample size should be sufficient to produce an 80% chance (power) of a significant result at a one-sided 0.025 significance level.

The non-inferiority margin "m" that characterizes the largest absolute difference considered to be dismissible is defined as 1.5. Since smaller values of NRS are better, the hypotheses are based on lower-tailed test:

H_0: $\mu_X(t) \geq \mu_M(t) + m$ vs H_A: $\mu_X(t) < \mu_M(t) + m$

Where: t is 24 weeks (6 months), μ_X is the NRS mean score in the Xpede arm, μ_M is the NRS mean score in the MENDEC and "m" is the non-inferiority margin.

Based on this statistical test and assuming a one-sided type I error rate of 0.025 and a type II error rate of 0.20 or equivalently, power of 0.80 for the final analysis, it will be claimed that Xpede is not inferior to MENDEC with respect to NRS score if the upper bound of the two-sided 95% confidence interval of the difference ($\mu_X(t)$ - $\mu_M(t)$) is less than the margin.

Thus, the non-inferiority hypothesis will require a sample size of 152 (76 per arm) subjects and including 15% of potential loss-to-follow-up, the total sample size for the study will be 179 . If we use 3 * 3 * 2 strata, the sample size should be 180 to be divisible of 18 (90 per arm).

13.2. Primary Objective #2 (Efficacy)

The second primary objective of this study is to demonstrate that the efficacy of XPEDE bone cement (Experimental group) is not inferior to the MENDEC (Control group) in terms of Index Vertebral Body Angles improvement at 24 weeks (6 months) postoperative from baseline.

13.2.1. Background

In Cancer Patient Fracture Evaluation (CAFE) study[16], the BKP patients' Index Spinal Deformity was measured by Index Vertebral Body Angles (VBA). The mean index VBA was 9.523 (8.751) at baseline and changed to 0.135 (5.088) and 0.954 (5.626) at respectively 1 month and 12 months .

[15] Copay AG, Glassman SD, Subach BR, Berven S, Schuler TC, Carreon LY. Minimum clinically important difference in lumbar spine surgery patients: a choice of methods using the Oswestry Disability Index, Medical Outcomes Study questionnaire Short Form 36, and pain scales. Spine J. 2008 Nov-Dec;8(6):968-74

[16] James Berenson, Robert Pflugmacher, Peter Jarzem, Jeff rey Zonder, Kenneth Schechtman, John B Tillman, Leonard Bastian, Talat Ashraf, Frank Vrionis, for the Cancer Patient Fracture Evaluation (CAFE) Investigators.

13.2.2. Sample Size Calculations

Sample size calculations were performed in SAS software (SAS Institute Inc., Cary, NC, USA). A sample size is determined such that the non-inferiority of the primary objective is demonstrated that results are not appreciably worse in XPEDE arm compared to MENDEC Spine arm. Based on this information the assumptions for the sample size are:

- The Angulation is assumed to be approximately normally distributed.
- The Angulation is to be assessed at 24 weeks (6 months) after the procedure.
- The Angulation at 24 weeks (6 months) is expected to be 1.2 in the MENDEC Spine treatment, and 1.2 or more in the XPEDE. A difference in Angulation of 2.5 or less is considered clinically unimportant for this comparison (half standard deviation rule). It is considered the maximum acceptable increase in Angulation compared to the MENDEC Spine arm. Standard deviation of 5.0 at 1 month from CAFÉ study was conservatively used to derive the non-inferiority margin of 2.5.
- The standard deviation of the Angulation is expected to be approximately 5.6 for both arms. Standard deviation of 5.6 at 12 months from CAFÉ study was conservatively used as the standard deviation for both arms.
- The sample size should be sufficient to produce an 80% chance (power) of a significant result at a one-sided 0.025 significance level.

The non-inferiority margin "m" that characterizes the largest absolute difference considered to be dismissible is defined as 2.5. Since smaller values of Angulation are better, the hypotheses are based on lower-tailed test:

H_0: $\mu_X(t) \geq \mu_M(t) + m$ vs H_A: $\mu_X(t) < \mu_M(t) + m$

Where: t is 24 weeks (6 months), μ_X is the mean of index VBA I in the XPEDE arm, μ_M is the mean of index VBA in the MENDEC and "m" is the non-inferiority margin.

Based on this statistical test and assuming a one-sided type I error rate of 0.025 and a type II error rate of 0.20 or equivalently, power of 0.80 for the final analysis, it will be claimed that XPEDE is not inferior to MENDEC with respect to Angulation if the upper bound of the two-sided 95% confidence interval of the difference ($\mu_X(t) - \mu_M(t)$) is less than the margin. Thus, the non-inferiority hypothesis will require a sample size of 160 levels treated and including 20% of potential loss-to-follow-up, the total sample size for the study will be 200 levels treated (100 per arm). Using the same distribution of treated levels from FREE trial: 72% with 1 level, 21% with 2 levels, 7% with 3 levels, the required subjects will be 200/1.35 = 148. If we use 3 * 3 * 2 strata, the sample size should be 162 to be divisible of 18 (81 per arm), which is smaller than what is required for the first primary objective.

Balloon kyphoplasty versus non-surgical fracture management for treatment of painful vertebral body compression fractures in patients with cancer: a multicentre, randomised controlled trial. Lancet Oncol 2011; 12: 225–356

13.3. Data analysis and reporting

The data will be collected from each center in the electronic Case Report Form (eCRF) data base via Oracle Clinic. A specific account number will be given to each center to access the system from any internet-enabled computer. Access to Internet is required for the sites to enter data into the system. User Identification codes will be created to identify data input from each center. The clinical data will be entered by the study staff and transmitted to the central database in an anonymous format so that the study sponsor will not be able to identify the patient, in accordance with the Chinese Data Privacy Directive. Electronic automatic and manual queries will be generated for missing, incorrect or doubtful data and sent directly to the study center via Oracle Clinic.

All the detailed data analyses are described in the Statistical Analysis Plan (SAP). Any change to the data analysis methods described in this section and/or the SAP will require an amendment only if it changes a principal feature of the study description. Any other changes to the data analysis methods will be described and justified in the Final Report or publication.

Based on the clinical practice in the surgery procedures and number of subjects enrolled per center, an investigation of center effect will be investigated including an independent variable for center in the model as well as summary statistics if needed.

13.4. Analysis of Clinical Data

Patient demographics and baseline characteristics will be presented using appropriate summary statistics. This includes mean and standard deviation, minimum, maximum and median with the interquartile range [IQR] for continuous variables, and counts and percentages for categorical variables. Summary statistics will be reported with maximum 2 decimals, as appropriate. The SAS software (SAS Institute Inc., Cary, NC, USA) or any other validated Statistical Software will be used to perform statistical analyses. The test for a treatment effect corresponds to showing that the upper bound of the two-sided 95% confidence interval (equivalent to the lower bound of a one-sided 97.5% confidence interval) for $\mu E(t)-\mu C(t) <$ margin. Graphical representations will be used as deemed appropriate. No adjustments for multiple comparisons or multiple look at data will be performed. Outliers and influential observations will be identified via graphical plots and according to study team decision and the analysis could be repeated excluding potential outliers. In case of missing data, the imputation of missing data will be performed using the most appropriate method depending on the pattern of missing in the data and the type of the imputed variable. After the imputation of the missing values the models will be rerun.

The data will be analyzed according to the intention-to-treat principle and a Full Analysis Set (FAS) will be used for primary final analysis. The FAS is the patient set containing all the patients included in the study that have signed the study Informed Consent and have received the study treatment. A secondary analysis could be performed on a Per Protocol Set (PPS). The PPS patients set containing all the patients that meet the inclusion/exclusion criteria with no other major protocol deviation that

could impact the clinic outcomes and have the 6 months follow-up visits completed. Any patient who does not satisfying the inclusion/exclusion criteria or receives the wrong treatment will be eliminate from the per-protocol population. Details of endpoints analyses and additional analysis will be described in the Statistical Analysis Plan.

The analyses based on freedom from event at 6 months will be described by means of Kaplan-Meier curves. Cox models will be fitted and hazard ratios (HRs) with 95% confidence intervals will be computed. The proportional hazard assumptions will be tested by means of Schoenfeld residuals. The exposure time (months) will be computed from the date of the index procedure to the date of the last available follow-up or date of first event: [(data end – data in)/30.4].

The rate of event will be computed and reported separately for each group, together with their 95% confidence intervals. Rates were compared by means of either a mixed Poisson model or a negative binomial regression model (if over dispersion was present). Incident rate ratios (IRRs) and 95% confidence intervals were used to compare the two groups.

Analysis of endpoints based on comparisons between groups on continuous measurements will be performed by Student's t-test or non-parametric test (Mann–Whitney U test) for normal and non-normal distributions, respectively. Normality will be assessed by means of Shapiro-Wilks test and the p-value will be reported. Categorical variable parameter comparisons will be performed using a Chi-square test, or a Mantel-Haenszel test for trend for ordinal variables with 3 or more categories.

The analysis on the first primary endpoint based on NRS will use one measure per patient and the comparison will be between the average NRS in both groups. It will be claimed that XPEDE is not inferior to MENDEC with respect to NRS score if the upper bound of the two-sided 95% confidence interval of the difference ($\mu_X(t)$ -$\mu_{M(}t)$) is less than the margin.

The analysis on the second primary endpoint based on Index Vertebral Body Angles will use multiple data points per patient according to the number of levels treated. Assuming not completely independence among measures within same patient the analysis will be performed by means of Generalized Estimating Equation (or mixed models for repeated measures) using patient as the subject. The model will have the Index Vertebral Body Angles as dependent variables and baseline value, number of level treated (as the multiple data points) and arm as explanatory variables. All assumptions for regression models will be assessed by viewing plots of the residual values. It will be claimed that XPEDE is not inferior to MENDEC with respect to Angulation if the upper bound of the two-sided 95% confidence interval of the difference ($\mu_X(t)$ -$\mu_M(t)$) is less than the margin.

The overall study is considered reached if both the null NI hypotheses are rejected. A separate Statistical Analysis Plan (SAP) will be developed prior to data being analyzed to further describe statistical methods, pre-specified data handling rules, and pre-specified analyses that will be included in the final study reports. Any deviation from the pre-specified statistical analyses will be noted in the study report.

The Statistical Analysis Plan will include a comprehensive description of the statistical methods and analyses to be included in reports that include analysis of endpoints. Any change to the data analysis methods described in the CIP will require an amendment only if it changes a principal feature of the CIP. Any other change to the data analysis methods described in the CIP, and the justification for making the change, will be described in the clinical study report.

14. Ethics

14.1. Statement(s) of Compliance

•This study is a pre-market clinical trial for product registration. The study will be conducted in accordance with the laws and regulations of China, including any future applicable laws and regulations in China.

•To protect the rights and welfare of patients, this clinical study will be conducted in compliance with the latest version of the Declaration of Helsinki (2013), the Clinical Trial Agreement (CTA) and Clinical Investigation Plan, the laws and regulations of China including Good Clinical Practice for Medical Devices (CFDA Order No. 25), Announcement of Chinese Regulation on Filing of Medical Device Clinical Trial (2015, No.87) and also including applicable data protection laws. Sites will also comply with any additional ethics committee requirements applicable.

•The sponsor will provide the medical institution with Medical Device Clinical Trial Notice

•The principles of the Declaration of Helsinki have been implemented through the patient informed consent (IC) process, Ethics Committee approval, study training, clinical trial registration, preclinical testing, risk-benefit assessment and publication policy.

•Approval of the CIP or CIP amendments is required from the following groups prior to any study procedures at a study site: Medtronic, principal investigators and Ethics Committee. Similarly, approval of subsequent revisions to the CIP is required at each study center from the above mentioned groups prior to implementation of the revised CIP at that center.

•Sponsor should be responsible for filing the study to Shanghai Municipal Food and Drug Administration after Ethics Committee approval of the current version of the CIP and fully executed Clinical Trial Agreement.

•All products will be labelled as per local regulations in China and products requiring investigational labelling will be labelled investigational as per local regulatory requirements.

•All participating study sites and investigators should make all the study data and study related records and including source data/records available for the monitoring, audits work from sponsor and inspection from EC and/or Regulatory body per their requirements to ensure the quality of the clinical trial.

•The sponsor shall avoid improper influence on, or inducement to, the subject, monitor, any investigator(s) or other parties participating in, or contributing to, the Xpede study.

•Sponsor representatives may provide support as required for the study, including technical support at site. Sponsor representatives may provide technical support as required for the study under supervision of the Principal Investigator, including:

•Provide study training relevant and pertinent to the involvement of personnel conducting study activities and investigator responsibilities.

Technical support will be under the supervision of a study investigator, but no data entry on the eCRF shall be performed by Medtronic personnel or their representatives at sites.

14.2. Ethics Committee (EC)

The study will be conducted in accordance with the requirements of local Ethics Committees. The responsible Ethics Committee (EC) at each investigational site must approve the study protocol and consent. Study activities will not commence prior to receipt of documentation of EC approval by the site and Medtronic. The Investigator and study site staff must comply with the requirements of their EC.

Prior to enrolling subjects, each investigational site's EC will be required to approve all necessary study documents including the CIP, the Informed Consent Form (ICF) and any other written information to be provided to the subjects. EC approval of the clinical study must be received in the form of a letter and provided to Medtronic before commencement of the study at an investigational site. The approval letter must contain enough information to identify the version or date of the documents approved. If this information is not contained in the approval letter, it must be retrievable from the corresponding submission letter. If the EC approval letter is not in English, the Medtronic clinical study team must ensure documented review of the letter in English, or a translation to English must be obtained. In addition, the approval letter needs to be accompanied by an EC roster or letter of compliance, to allow verification that the investigator, other site study staff, and/or Medtronic personnel are not members of the EC. If they are members of the EC, written documentation is required stating that he/she did not participate in the approval process. Medtronic will prepare the required documents and send them to the investigator for reporting to the EC. Investigators must inform Medtronic of any change in status of EC approval once the investigational site has started enrollment. If any action is taken by an EC with respect to the investigation, that information will be forwarded to Medtronic by the respective investigator.

14.2.1. General Study Requirements

Prior to enrolling any subjects in the study, all requirements need to be fulfilled. Each site must have written documentation of site/Investigator readiness, including but not limited to EC approval, a signed investigator agreement, and site research personnel training documentation. The Investigators shall agree to this protocol and any amendments by signing and dating the investigator agreement.

The participating Investigator is responsible for adhering to this CIP, the Declaration of Helsinki

2013, the agreement and the applicable local regulatory requirements.

14.2.2. Informed Consent and Ethics Committees

All subjects must provide written informed consent in accordance with approved by the site's EC and Medtronic. A copy of the informed consent form from each site must be forwarded to Medtronic for review and approval prior to submitting it to the EC. A sample copy of the informed consent form is provided in Appendix 4. Each site must provide Medtronic with a copy of the investigational site's EC approval letter and the EC approved informed consent form. Approvals for the continuation of the study at each investigational site must be kept current and notifications forwarded to Medtronic.

14.3. Monitoring

Medtronic monitors the regulatory and reporting compliance of clinical studies to ensure the overall integrity and quality of the data through a combination of the following actions:

- Automated data logic checks
- Statistical analysis to identify data trends or anomalies
- Statistical analysis to identify sites that are outliers relative to other participants
- Source verification using available in-house data e.g. data transmission
- Regulatory and reporting compliance trends
- Interim on-site clinical monitoring visits
- Site Audits

It is the responsibility of Medtronic to ensure proper monitoring of this study per regulations. Trained Medtronic personnel or delegates appointed by Medtronic may perform study monitoring activities to ensure this study is conducted in accordance with the protocol, Clinical Trial Agreement, and applicable regulatory and local requirements.

Medtronic (or delegates) must be allowed access to the subjects' case histories when conducting onsite interim monitoring visits (clinic and hospital records, and other source data/documentation) upon request as per the Informed Consent Form, Research Authorization (where applicable) and Clinical Trial Agreement.

Site Monitoring Visits

Frequency of onsite monitoring visits will be based upon subject enrollment, duration of the study, compliance, number of adverse events or deviations, findings from previous monitoring visits and any suspected inconsistency in data that requires investigation. Regulatory documents may be reviewed at each site. Monitoring for the study, including site qualification visits, site initiation visits,

interim monitoring visits, and closeout visits, will be done in accordance to the study-specific monitoring plan.

Visits may be conducted periodically to assess site study progress, the investigator's adherence to study requirements regulatory compliance including but not limited to IRB approval and review of the study, maintenance of records and reports, and review of source documents against subject CRFs. Monitors review site regulatory and study compliance by identifying findings of non-compliance and communicating those findings along with recommendations for preventative/corrective actions to site personnel. Monitors may work with study personnel to determine appropriate corrective action recommendations and to identify trends within the study or at a particular site.

Further details of monitoring and a list of data which can be recorded directly in the CRF will be given in the study specific monitoring plan. The Monitoring Plan will be provided under a separate cover

14.4. Data Management

Data will be collected using an electronic data management system. Data reporting will be completed and submitted by the clinician or authorized staff. All data will be stored in a secure, password-protected database.

Medtronic will review site reported data to monitor data quality, data discrepancies will be created as required and forwarded to the site for resolution. Study management reports may be generated by Medtronic to monitor data quality and study progress. Site personnel are responsible for the timely submission of data and the resolution of discrepancies.

Reported data elements should be supported in the subject's case history. Any time the database reported data are the only record, it should be appropriately documented. In these cases, an alternate method of source documentation is highly recommended.

For products capable of transmitting data, device data uploads/transmissions will be collected for Medtronic products only. This data will be obtained directly from the submitted device file (i.e. transmission, etc.) therefore, additional source verification will not be required.

Medtronic or regulatory authority may audit the site to evaluate the conduct of this study. The Investigator(s)/institution(s) shall allow study-related monitoring, audits, EC/IRB review, and regulatory inspection(s) by providing direct access to study source data/documents, and regulatory documents.

Leading site will be accountable for data management and analysis about the data from each clinical research institution in a centralized manner according to local regulations and study requirements. Medtronic will oversee all data management functions and provide support if necessary.

14.5. Direct Access to Source Data/Documents

When source data verification is performed, the monitor must have direct access to original source documentation and/or certified copies of the original source must be provided. Subject completed questionnaires are self-reported source documents and data is to be entered into the RDC by the site staff directly from the completed original questionnaires.

If applicable, the Investigator(s)/Institution(s) will permit study-related monitoring, audits, IRB/EC review, and regulatory inspection(s), providing direct access to original source data/documents and/or certified copies of the original source.

Where printouts of electronic medical records, are provided as source documents, or where copies of source documents are retained as source documents, they should be signed and dated by a member of the investigation site team indicating they are a true reproduction of the original source document.

The eCRFs will not serve as source documents. Source documentation for data elements not routinely captured in medical records may vary from site to site: the site may use worksheets if identified as source documents.

15. Study Administration

15.1. Confidentiality

All records and other information about subjects participating in this study will be treated as confidential. Data will be transferred and processed by Medtronic or a third party designated by Medtronic in a key coded form, unless it's impossible to make it anonymous, for instance, where the patient's name cannot be removed from the data carrier, such as fluoroscopy images.

Procedures in the CIP require source documentation. Source documentation will be maintained at the site. Source documents, which may include worksheets, patient medical records, programmer printouts, and interrogation files, must be created and maintained by the investigational site team.

Medtronic or regulatory authority may audit the site to evaluate the conduct of this study. The Investigator(s)/institution(s) shall allow study-related monitoring, audits, EC/IRB review, and regulatory inspection(s) by providing direct access to study source data/documents, and regulatory documents.

15.2. Liability

If subjects are physically injured as a result of participation in this study, reasonable and appropriate medical treatment will be provided by Medtronic, if such treatment is not already covered by subject's medical insurance according to the local requirements. The local sponsor Medtronic (Shanghai) Management Co, Ltd. is a wholly owned subsidiary of Medtronic, Inc., which as the parent company of such entity maintains appropriate clinical study liability insurance coverage as required under applicable laws and regulations and will comply with applicable laws and customs concerning specific insurance coverage. If required, a Clinical Study Insurance statement/certificate will be provided to the EC.

Funding for the study will be defined according to the local regulations and must be agreed upon in writing by the clinical research institution and Medtronic before the study commences. The payments for the study should be appropriate relative to the number of subjects enrolled. The Kyphon®Xpede™ Bone Cement will be provided by Medtronic free of charge for use in this clinical study. A reasonable amount of the procedures outside the routine practice done for this clinical study will be reimbursed. No any other compensation for the participation in this study will be received.

15.3. Finance

Funding for the study will be defined according to the local regulations and must be agreed upon in writing by the clinical research institution and Medtronic before the study commences. The payments for the study should be appropriate relative to the number of subjects enrolled . The Xpede bone cement and the Mendec will be provided by Medtronic free of charge for use in this clinical study.

15.4. CIP Amendments

Approval of the CIP or CIP amendments is required from the following groups prior to any study procedures at a study site: Medtronic, principal investigators, geography-specific regulatory authorities (if regulatory approval is required) and an independent Ethics Board. Similarly, approval of subsequent revisions to the CIP is required at each study center from the above mentioned groups prior to implementation of the revised CIP at that center.

15.5. Responsibilities of all Parties

Investigator responsibilities will be included in clinical trial agreement and subject responsibilities will be available in Informed Consent Form (ICF). Sponsor will undertake all the responsibilities of the sponsor as required per local regulations.

15.6. Record Retention

15.6.1. Investigator Records

The investigator is responsible for the preparation and retention of the records cited below. All of these records, with the exception of case history records and case report forms, should be kept in the Investigator Site File (i.e., the study binder provided to the investigator) or Subject Study Binder. CRFs may be maintained and signed electronically within the electronic data capture system during the study. Clinical trial institutions shall keep the clinical trial data for at least ten years after the completion of clinical trials.

- All correspondence between the EC, sponsor, monitor, NMPA /regulatory authority and or the investigator that pertains this study
- Subject identification and enrollment log, and subject screening log, where required per local law Subject's case history
    - Informed Consent
    - Observations of AEs/ADEs/DDs
    - Medical history
    - procedure and follow-up data
    - Documentation of the dates and rationale for any deviation
- All approved versions of the CIP, Informed Consent Form
- Signed and dated Clinical Trial Agreement
- Delegation documentation
- Study training records for site staff
- Any other records that NMPA and local regulatory agencies require to be maintained.
- Final Study Report including the statistical analysis
- Current Signed and dated CV of PI (and key study team members if required per local requirements)
- Device accountability records, Shipping records for investigational devices and clinical–investigation related documents and materials
- Software disposition logs
- Electronically signed and dated CRFs

15.6.2. Investigator Reports

The investigator is responsible for the preparation (review and signature) and submission to the sponsor of all case report forms, adverse events and adverse device effects (reported per the country-specific collection requirements), device deficiencies, deaths, and any deviations from study requirements. If any action is taken by an EC/IRB with respect to this study, copies of all pertinent documentation must be forwarded to Medtronic in a timely manner. Reports are subject to inspection and to the retention requirements as described above for investigator records.

Table 9: Investigator Reports per Medtronic Requirements

Report	Submit to	Description/Constraints
Clinical trial institution and Investigator Initiated Study suspension or termination	Local NMPA	If it is required to suspend or terminate the trial as the clinical trial institution and investigators found that the risk outweighs the possible benefits or results have been obtained that suffice the judgment of the safety and effectiveness of medical device, the investigators shall inform the subjects, and make sure appropriate treatment and follow-up visits for the subjects, and meanwhile report as required with detailed written explanation for the suspension and termination. Report to the food and drug regulatory authorities of the provinces, autonomous regions and municipalities directly under the central government if necessary. *(GCP for Medical Devices, CFDA order No.25 Article 76)*
Failure to obtain informed consent	Sponsor and Ethics Committee	Informed consent shall be obtained in writing and documented before a subject is enrolled into the clinical investigation. *(ISO 14155:2011)*

Safety Report	Clinical Trial Institution Sponsor, Local FDA or Regulatory Authority	For the serious adverse events occurred in clinical trials, investigators shall immediately adopt appropriate therapeutic measures for subjects, and simultaneously report to the management department of medical device clinical trials in clinical trial institutions in written form, and notify the sponsor in written form. Management department of medical device clinical trials shall report to corresponding Ethics Committee as well as local food and drug regulatory authority and health and family planning regulatory authority of the province, autonomous region and municipality directly under the central government where the clinical trial institution locates in written form within 24 hours. In case of death of subjects, the investigators and clinical trial institutions should provide all the required additional information to the Ethics Committee and the sponsor. *(GCP for Medical Devices, CFDA order No.25 Article 71)*
Deviation and Progress report	Management Department of Medical Device	Study deviations and progress report should be submitted to Management department of medical device clinical study then they will submit to Sponsor and EC

Final report	NMPA, Sponsor, and Clinical Trial Institution	Upon completion of multi-center clinical trials, investigators of all clinical trial institutions shall issue brief summary of clinical trials, respectively, and submit it to coordinating investigator together with Case Report Form upon review as required for coordinating investigator to summarize and complete summary report. *(GCP for Medical Devices, CFDA order No.25 Article 29（7）)* Investigators should, in accordance with the design requirements of the clinical trial protocol, verify and validate the safety and effectiveness of investigational medical devices, and complete the Clinical Trial Report. As for multi-center clinical trials, the Clinical Trial Report should contain the Summaries of Clinical Trial of all sub-centers. *(GCP for Medical Devices, CFDA order No.25 Article 83)* The Clinical Trial Report should be signed and dated by the investigators, and submitted to the sponsor after being reviewed, commented, dated and sealed by medical device clinical trial administration department of clinical trials institutions. For multi-center clinical trial, the clinical trial summary of each center should be signed and dated by the investigators of respective center, and submitted to the leading site after being reviewed, dated and sealed by the site's clinical trial administration department. *(GCP for Medical Devices, CFDA order No.25 Article 86)*

15.6.3. Medtronic Records

Medtronic shall maintain the following (but not limited to) accurate, complete, and current records:

- All correspondence which pertains to the studies
- Investigational device tracking documentation
- Signed Clinical Trial Agreements and delegation documentation as well as the signed agreements with third party(if applicable) and FD from PI

- All electronically signed and dated case report forms submitted by investigator, including reports of AEs, ADEs and Device Deficiencies, Subject Deaths
- All approved Informed Consent Forms, and other information provided to the subjects and advertisements, including translations
- Copies of all EC/IRB approval letters and relevant EC/IRB correspondence and EC/IRB voting list/roster
- Names of the institutions in which the Study will be conducted
- Names/contact addresses of monitors
- Statistical analyses and underlying supporting data
- Study final reports
- Sample eCRFs
- All versions of the study protocol and IB
- Training records of site personnel and Medtronic personnel involved in the study
- Sample of labelling attached to investigational products
- Any other records required by the NMPA

15.6.4. Medtronic Reports

Medtronic shall prepare and submit the following complete, accurate, and timely reports listed in the tables below. In addition to the reports listed below, Medtronic shall, upon request of reviewing EC/IRB or NMPA or local regulatory authority, provide accurate, complete and current information about any aspect of the respective study.

Table 10: Sponsor Reports

Report	Submit to	Description/Constraints
Premature termination or suspension of the clinical investigation	Clinical Trial Institution Investigator Ethical Committee Local Regulatory Authority	For deciding to suspend or terminate clinical trials, sponsor shall notify the management department of medical device clinical trials of all clinical trial institutions within 5 days, and state the rational in written form. Management department of medical device clinical trials in clinical trial institutions shall timely notify corresponding investigators and Ethics Committee. The suspended clinical trials shall not be recommenced without the approval of Ethics Committee. Upon the completion of clinical trials, sponsor shall notify local food and drug regulatory authority of the province, autonomous region and municipality directly under the central government where he locates in written form. *(GCP for Medical Devices, CFDA order No.25 Article 46)*

Safety Report	Local FDA or Regulatory Authority Clinical Trial Institution Investigator Ethical Committee	For serious adverse events or the device deficiencies possibly resulting in serious adverse events, sponsor shall report to the food and drug regulatory authorities and health and family planning competent authorities at the same level filed within 5 working days upon being informed, simultaneously notify other clinical trial institutions and investigators participating in the trial, and timely report to Ethics Committee of the clinical trial institution through management department of medical device clinical trials.
Final report	Investigators, NMPA, local competent authority	The Clinical Trial Report should be signed and dated by the investigators, and submitted to the sponsor after being reviewed, commented, dated and sealed by medical device clinical trial administration department of clinical trials institutions. For multi-center clinical trial, the clinical trial summary of each center should be signed and dated by the investigators of respective center, and submitted to the leading site after being reviewed, dated and sealed by the site's clinical trial administration department. *(GCP for Medical Devices, CFDA order No.25 Article 86)* *Sponsor will submit the final report to NMPA after obtaining it from the medical institution.*

Medtronic records and reports will be stored in secure file cabinets at Medtronic during the course of the study. Electronic versions of the reports will be kept on a password-protected document management system. After closure of the study, all records and reports will be archived indefinitely

15.7. Publication and Use of Information

Publications based on the results of the study will follow the process outlined in the Clinical Study Agreement.

15.8. Suspension or Early Termination

15.8.1. Planned Study Closure

Study Closure is a process initiated by distribution of an initial study closure letter. Study closure is defined as closure of a clinical study that occurs when Medtronic and/or regulatory requirements have been satisfied per the protocol and/or by a decision by Medtronic or regulatory authority, whichever occurs first. The study closure process is complete upon distribution of the Final Report or after final payments, whichever occurs last. Ongoing IRB oversight is required until the overall study closure process is complete.

15.8.2. Early Termination or Suspension

Early Termination of the study is the closure of a clinical study that occurs prior to meeting defined endpoints. This is possible for the whole study or a single site. Study Suspension is a temporary postponement of study activities related to enrollment and distribution of the product. This is possible for the whole study or a single site.

Study-Wide Termination or Suspension

Possible reasons for considering study suspension or termination of the study include but are not limited to:

- Adverse events associated with the system or product under investigation which might endanger the safety or welfare of the subject
- Observed/suspected performance different from the product's design intent
- Decision by Medtronic (circumstances include but are not limited to; interests of the health of the study subjects, continuation of the study cannot serve any scientific purpose, insolvency) or regulatory body (where the study is operating under regulatory body authority)
- Technical issues during the manufacturing process

Investigator/Site Termination or Suspension

Possible reasons for clinical investigator or site termination or suspension include but are not limited to:

- Failure to obtain initial IRB approval or annual renewal of the study
- Persistent non-compliance to the clinical investigation (e.g. failure to adhere to eligibility criteria, failure to follow subjects per the scheduled follow-ups)
- Lack of enrollments

- Noncompliance to regulations and the terms of the Clinical Trial Agreement (e.g. failure to submit data in a timely manner, failure to follow-up on data discrepancies and monitoring findings in a timely manner, etc.)
- IRB suspension
- Fraud or fraudulent misconduct is discovered
- Investigator request (e.g. no longer able to support the study)

15.8.3. Procedures for Suspension or Termination

Medtronic-Initiated

- For deciding to suspend or terminate clinical trials, sponsor shall notify the management department of medical device clinical trials of all clinical trial institutions within 5 days, and state the rationale in written form.
- Management department of medical device clinical trials in clinical trial institutions shall timely notify corresponding investigators and Ethics Committee.
- The suspended clinical trials shall not be recommenced without the approval of Ethics Committee.
- Upon the completion of clinical trials, sponsor shall notify local food and drug regulatory authority of the province, autonomous region and municipality directly under the central government where he locates in written form.
- Upon receipt of notification of suspending or terminating clinical trials from sponsor, investigators shall timely notify subjects and ensure that subjects receive appropriate treatment and follow-up.
- In the case of a study suspension, subject enrollment must stop until the suspension is lifted by Medtronic with the approval of Ethics Committee.
- In the case of a study suspension, enrolled subjects should continue to be followed out of consideration of their safety, rights and welfare.

Clinical Trial Institution and Investigator-Initiated

- If it is required to suspend or terminate the trial as the clinical trial institution and investigators found that the risk outweighs the possible benefits or results have been obtained that suffice the judgment of the safety and effectiveness of medical device, the investigators shall inform the subjects, and make sure appropriate treatment and follow-up visits for the subjects, and meanwhile report as required with detailed written explanation for the suspension and termination.

- Clinical Trial Institution and Investigator shall report to the food and drug regulatory authorities of the provinces, autonomous regions and municipalities directly under the central government if necessary.
- In the case of a study suspension, subjects enrolled should continue to be followed out of consideration of their safety, rights and welfare.

EC/IRB-Initiated

- The investigator will inform Medtronic and provide a detailed written explanation of the termination or suspension within 5 business days
- Subject enrollment must stop until the suspension is lifted
- Subjects already enrolled should continue to be followed in accordance with Ethics
- Committee policy or its determination that an overriding safety concern or ethical issue is involved
- The investigator will inform his/her institution (where required per local requirements)
- Upon receipt of notification of suspending or terminating clinical trials from Ethics Committee, investigators shall timely notify subjects and ensure that subjects receive appropriate treatment and follow-up.

16. Appendixes

Appendix : Study Contact

Sponsor:	Medtronic SOFAMOR DANEK USA 1800 Pyramid Place, Memphis, TN USA 38132.
Local Sponsor:	Medtronic (Shanghai) Management Co., Ltd. 11F, Building B, No 5, Lane 255, DongYu Road, Pudong, Shanghai
Clinical Operations:	Medtronic Inc CHN Medtronic Core Clinical Solutions 11F, Building B, No 5, Lane 255, DongYu Road, Pudong, Shanghai
Monitoring:	Medtronic Inc CHN Medtronic Core Clinical Solutions 11F, Building B, No 5, Lane 255, DongYu Road, Pudong, Shanghai

The detailed contact list will be kept separate from the CIP and provided to the Investigators. Medtronic will maintain an updated list. For specific contact information of the core members refee to the detailed list.

For the relevant qualification documents of Medtronic refer to the EC review document package.

Appendix A: Informed Consent Form

The ICF template will be provided under a separate cover.

Version History

Version	Summary of Changes	Author(s)/Title
1.0	• New Document	Tristan Zhao, Clinical Research Sr. Manager Laura Manotta, EMEA RCC Principal Proj and Clinical Research Spec
2.0	• Updated indication for Use according to M708348B093E Rev C • Correction of minor typos	Laura Manotta, EMEA RCC Principal Proj and Clinical Research Spec
3.0	• Update inclusion criteria: age range between 18-80 years • Specification that the efficacy will be evaluated by a blinded investigator • Definition of a central image reading CoreLab • Removal of the CEC as not required by local regulation	Laura Manotta, EMEA S&SS Principal Proj and Clinical Research Spec