Summary of Safety and Clinical Performance (SSCP): CR 336
Revision: 0
Effective Date: 03-Nov-2022

Summary of Safety and Clinical Performance (SSCP) for Intended Users/Healthcare Professionals:

i≡FACTOR Putty

i≡FACTOR Flex FR

Sponsor:
Cerapedics, Inc.
11025 Dover Street, Suite 1600
Westminster, CO 80021 USA

This Summary of Safety and Clinical Performance (SSCP) is intended to provide public access to an updated summary of the main aspects of the safety and clinical performance of the device.

The SSCP is not intended to replace the Instructions For Use as the main document to ensure the safe use of the device, nor is it intended to provide diagnostic or therapeutic suggestions to intended users or patients.

Refer to CR 340, revision 0 for User Instructions for Use, Implant Card Instructions, and SSCP Readability Validation Report of this document.

The English version of this SSCP document (CR 336) has been validated by the notified body (#2797).

Following this information there is a summary intended for patients.

Abbreviations

ABM	Anorganic bone mineral
ACDF	Anterior cervical discectomy and fusion
AE	Adverse event
AIDS	Autoimmune Deficiency Syndrome
ALIF	Anterior lumbar interbody fusion
ASD	Adult spinal deformity
BMPs	Bone morphogenetic proteins
BSE	Bovine Spongiform Encephalopathy
BSR	British Spine Registry
CE (mark)	Conformitè Europëenne
CS	Common Specifications
CT	Computed tomography
DBM	Demineralized bone matrix
DCS	Delayed cage subsidence
DDD	Degenerative disc disease
DLIF	Direct lateral interbody fusion
EMDN	European Medical Device Nomenclature
EQ-5D	European Quality of Life Five Dimension
FDA	Food and Drug Administration
Fe	Iron
FR	Fiber reinforced
FSCA	Field safety corrective action
FSN	Field safety notice
GMDN	Global Medical Device Nomenclature
HAs	Hydroxyapatites
HIV	Human Immunodeficiency Virus
HO	Heterotopic ossification
HRQoL	Health-related quality of life
ID	Identification
IDE	Investigational device exemption
IFU	Instructions for use
IIS	Investigator-initiated study
LFCN	Lateral femoral cutaneous nerve
MCID(s)	Meaningful Clinically Important Difference(s)
MCS	Mental Health Composite Score/Mental Component Summary/Mental Health Component Score
MDD	Medical Device Directive
Mg	Magnesium
MRI	Magnetic resonance imaging
NA	Not applicable
NaCMC	Sodium carboxymethylcellulose
NB	Notified Body
NDI	Neck Disability Index
NS	Not specified
ODI	Oswestry disability index
P-15	Synthetic collagen fragment
PAO	Periacetabular osteotomy
PCS	Physical Composite Score/Physical Component Summary/Physical Health Composite Score/Physical Component Score/Physical Health Component Score
PLF	Posterior lumbar fusion

PLIF	Posterior lumbar interbody fusion
PMA	Premarket Approval
PMCF	Post-market clinical follow-up
PMS	Post-market surveillance
PROMs	Patient reported outcome measures
QoL	Quality of life
RCT	Randomized controlled trial
rRhBMP-2	Recombinant Human Bone Morphogenetic Protein-2
SAE	Serious adverse event
SF-12	Short form-12
SF-36	Short Form 36
SF-36v2	Short Form 36 v2
SRN	Single Representative Number
SRS-22	Scoliosis Research Society-22
SSCP	Summary of Safety and Clinical Performance
TCP	Tricalcium phosphate
TGF-β	Transforming growth factor beta
TLIF	Transforaminal lumbar interbody fusion
UDI-DI	Unique Device Identification-Device Identifier
US	United States
USA	United States of America
VAS	Visual Analog Scale
Zn	Zinc

1. Device identification and general information

1.1. Device trade name(s)

i≡FACTOR® Putty, i≡FACTOR® Flex FR

Product Code	Description
900-010	i≡FACTOR® Putty, 1.0 cc
900-025	i≡FACTOR ® Putty, 2.5 cc
900-050	i≡FACTOR ® Putty, 5.0 cc
900-100	i≡FACTOR ® Putty, 10.0 cc
950-012	i≡FACTOR ® Flex FR, 12 mm
950-025	i≡FACTOR ® Flex FR, 25 mm
950-050	i≡FACTOR ® Flex FR, 50 mm
950-100	i≡FACTOR ® Flex FR, 100 mm

Both i≡FACTOR Putty and i≡FACTOR Flex FR are part of the same device family, referred to as i-FACTOR, i≡FACTOR, i≡FACTOR product(s), i≡FACTOR Bone Graft(s), i≡FACTOR Bone Graft device(s), i≡FACTOR Bone Graft Product(s) or i≡FACTOR Peptide Enhance Bone Graft(s).

1.2. Manufacturer's name and address

Cerapedics Inc.
11025 Dover Street, Suite 1600
Westminster, CO 80021
USA

1.3. Manufacturer's single registration number (SRN)

US-MF-000008759

1.4. Basic UDI-DI

0085000168

1.5. Medical device nomenclature description / text

The European Medical Device Nomenclature (EMDN) code for i≡FACTOR products is P900402 - resorbable filling and reconstruction devices. In the Global Medical Device Nomenclature (GMDN) System, i≡FACTOR products have the designated primary code number 46425. The terms associated with this device is "bone matrix implant, animal derived, bioabsorbable".

1.6. Class of device

Class III

1.7. Year when the first certificate (CE) was issued covering the device

i≡FACTOR Putty – 2008

i≡FACTOR Flex FR - 2014

1.8. Authorised representative if applicable; name and the SRN

Emergo Europe B.V.

SRN: NL-AR-000000116

1.9. NB's name (the NB that will validate the SSCP) and the NB's single identification number

BSI Group The Netherlands B.V.

NB single identification number: 2797

2. Intended use of the device

2.1. Intended purpose

i≡FACTOR Bone Graft is a bone graft substitute material intended to provide bony ingrowth and fusion in gaps and voids.

2.2. Indication(s) and target population(s)

i≡FACTOR Putty

i≡FACTOR Putty is a bone substitute material for use in arthrodesis of the spine and foot and ankle.

Spinal arthrodesis is defined as the elimination of motion across an intervertebral segment as a result of bony union and may be required as a result of degenerative spinal disorders, spinal deformities or pathologic spine changes secondary to trauma, tumour, infection, and inflammatory or metabolic disorders.

Foot and ankle arthrodesis is defined as the elimination of motion across tibiotalar joint and joints in the foot as a result of bony union and may be required as a result of degenerative disorders and pathologic changes secondary to arthritis, trauma, tumour, infection, and inflammatory or metabolic disorders.

i≡FACTOR Flex FR

i≡FACTOR Flex FR is a bone substitute material for use in arthrodesis of the spine.

Spinal arthrodesis is defined as the elimination of motion across an intervertebral segment as a result of bony union and may be required as a result of degenerative spinal disorders, spinal deformities or pathologic spine changes secondary to trauma, tumour, infection, and inflammatory or metabolic disorders.

Target populations

Adult or skeletally mature, male or non-pregnant female

2.3. Contraindications and/or limitations

- Absence of load bearing structural support at the graft site
- Sensitivity to components of the i≡FACTOR Bone Graft (including allergies to silk for the i≡FACTOR Flex FR)
- Active infection at the operative site
- Operative site subject to excessive impact or stress
- Significant vascular impairment proximal to the graft site
- Use in direct contact with articular spaces
- Presence of segmental defects
- Metabolic or systemic bone disorders that affect bone or wound healing
- Compromised renal function
- Uncooperative patients who will not or cannot follow postoperative instructions, including individuals who abuse drugs and/or alcohol

3. Device description

3.1. Description of the device

i≡FACTOR Bone Graft is a composite bone substitute product consisting of a synthetic collagen fragment (P-15) adsorbed onto calcium phosphate particles (hydroxyapatite), which are suspended in an inert hydrogel carrier (sodium carboxymethylcellulose (NaCMC)/glycerin/water). The bovine derived calcium phosphate particles, also known as anorganic bone mineral (ABM), provide a scaffold and source of calcium for new bone growth. The bovine-derived ABM particles within the scaffold are radiopaque and sized between 250 and 425 microns. i≡FACTOR consists of ABM/P-15 particles that are suspended in an inert biocompatible hydrogel. The synthetic collagen fragment (P-15) is a short chain peptide that mimics a cell binding domain of Type I collagen, thus providing a more favourable environment that facilitates osteogenic cell attachment to the ABM scaffold. Osteogenic cells are “anchorage-dependent”, meaning that they must firmly adhere and spread onto a surface to enable their survival and growth. The P-15-coated ABM surfaces provide an abundance of binding sites which promote cell attachment and spreading across the ABM surface thereby reducing the risk of apoptosis (programmed cell death) and providing a survival advantage compared to non-coated surfaces. P-15 binding to cell surface sites (integrins) stimulates transmembrane signals to the cell’ cytoskeleton activating focal adhesion enzymes that amplify natural signalling pathways important for bone regeneration including increased expression of bone morphogenic proteins and cytokines. Enhanced secretion of these factors contributes to enhanced cell proliferation, attraction of further cells and heightened differentiation to support cellular infiltration of the graft. The ABM/P-15 particles are the functional component of the bone graft, whereas the hydrogel acts as a carrier, aiding in the placement and containment of the particles at the graft site. After implantation, the hydrogel is

resorbed, and the ABM/P-15 particles are concomitantly enveloped by cells, stabilized by new tissues and eventually remodelled into native bone via cell mediated bone resorption and deposition. The devices are designed to be implanted in bony voids and gaps in which the devices are not intrinsic to the mechanical stability of the healing environment.

i≡FACTOR products are available in two product variations:

i≡FACTOR Putty and i≡FACTOR Flex FR (Figure 1).

i≡FACTOR Putty, as the name states, has a putty like consistency. i≡FACTOR Flex FR is a lyophilized (freeze-dried) version of the i≡FACTOR Putty that has been formed into flexible rectangular strips. The Flex FR product also contains a small quantity of purified silk fibroin fiber segments that provides graft cohesiveness and alternate handling characteristics of the lyophilized strip compared to Putty. The 'FR' acronym in the product name represents "Fiber Reinforced".

Both i≡FACTOR Putty and i≡FACTOR Flex FR are for single-use only. Both are sterilized using steam and single sterile barrier system with protective packaging inside.

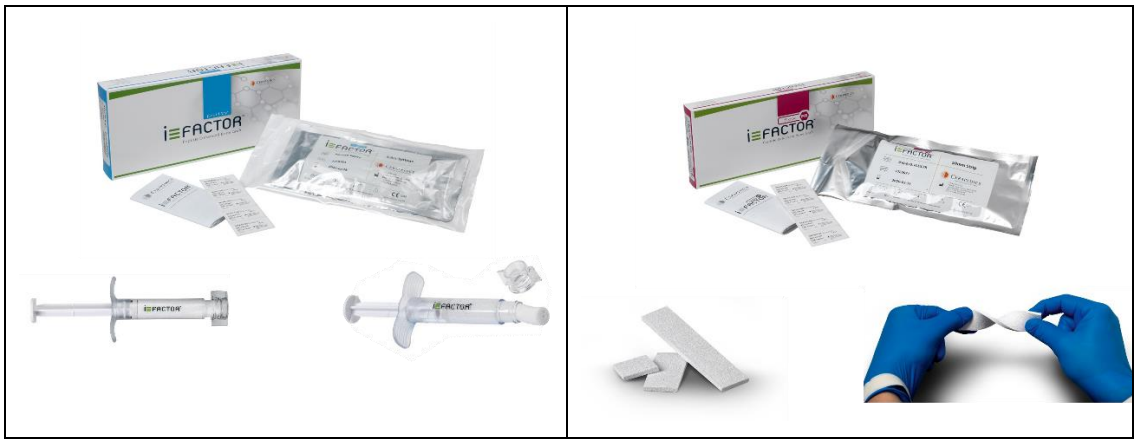


FIGURE 1: I≡FACTOR PUTTY (LEFT) AND I≡FACTOR FLEX FR (RIGHT)

3.2. A reference to previous generation(s) or variants if such exist, and a description of the differences

There have been no changes to the design of the i≡FACTOR Putty or i≡FACTOR Flex FR since they were launched. An additional variant, i≡FACTOR Flex was developed to provide an additional form-factor of i≡FACTOR to users and was available from 2010 to 2017. i≡FACTOR Flex was a lyophilized (freeze-dried) version of the i≡FACTOR Putty. i≡FACTOR Flex was superseded by i≡FACTOR Flex FR which provides improved cohesiveness and flexibility. i≡FACTOR Flex FR is a lyophilized (freeze-dried) version of the i≡FACTOR Putty that has been formed into rectangular strips, containing a small quantity of purified silk fibroin fiber segments.

3.3. Description of any accessories which are intended to be used in combination with the device

Not applicable. There are no accessories intended to be used with the i≡FACTOR Putty or -FACTOR Flex FR.

3.4. Description of any other devices and products which are intended to be used in combination with the device

Not applicable. There are no other devices and products which are intended to be used in combination with the i≡FACTOR Putty or i≡FACTOR Flex FR.

4. Risks and warnings

4.1. Residual risks and undesirable effects

Cerapedics searches for risks or side-effects when i≡FACTOR bone grafts are used, and reduces these risks with various methods, deciding the risk level of the device and individual risks as part of the risk management process. Undesirable effects/residual risks are described in the table below. The expected frequency is based on analysis of complaints and post-market surveillance (PMS) data, rates reported in post-market clinical follow-up (PMCF) studies and/or rates reported in the scientific literature. A time frame is provided for each estimate of frequency. This is the time (length of follow-up) after implantation/use at which data was collected to be used in the estimation of frequency.

These have been covered appropriately in the instructions for use (IFU) for both devices (adverse effects).

Should the patient believe they are experiencing side-effects related to the device or its use, it is advised that they consult their doctor/surgeon.

TABLE 1: RESIDUAL RISKS FOR I≡FACTOR PUTTY AND I≡FACTOR FLEX FR

Undesirable effect / residual risk	Device	Anatomical location	Time frame	Expected frequency/ quantification	Source	Discussion
Failure to achieve bone fusion (nonunion, malunion or delayed union)	i≡FACTOR Putty	Spine	Post-operatively; 3 months to 6 years	Overall - <0.01-12.50% Leading to negative impact/requiring reintervention or reoperation – 3.70%	• Clinical Investigation Data (Food and Drug Administration (FDA) investigational device exemption (IDE) study) • PMCF study data • Literature search (i.e. literature on the subject devices) • Data generated from complaints/spontaneously reported events and may be underreported (i.e. on the subject devices) • Public vigilance databases (on subject devices, incidence rate not available from public vigilance database data)	Failure to achieve fusion (pseudarthrosis) may result in a deterioration in patient status which may result in the need for additional clinical care or surgical revision. Whether or not non-union leads to a negative clinical impact or the need for reoperation/reintervention is not often specified in studies. The fusion potential for i≡FACTOR products has been subject to extensive evaluation in numerous studies and has been proven to offer similar or superior fusion outcomes relative to other bone graft materials, including autograft and allograft. Overall non-union is reported with comparators at rates up to 48% up to 6 years follow-up.
	i≡FACTOR Flex FR	Spine		Overall - <0.01% Leading to negative impact/requiring reintervention or reoperation – not reported	• Data generated from complaints/spontaneously reported events and may be underreported (i.e. on the subject devices)	

Undesirable effect / residual risk	Device	Anatomical location	Time frame	Expected frequency/ quantification	Source	Discussion
	i≡FACTOR Putty	Foot and ankle	Post-operatively; 12 months follow-up	Overall - 0-4% Leading to negative impact/requiring reintervention or reoperation – 0-4%	• Data generated from complaints/spontaneously reported events and may be underreported (i.e. on the subject devices) • PMCF study data	Non-union leading to a negative clinical impact or the need for reoperation/reintervention is reported with comparators at rates up to 14% up to 6 years follow-up.
Failure due to product migration	i≡FACTOR Putty	Spine	Intra-operatively Post-operatively; up to 6 years	Overall - 0-4.65% Leading to negative impact/requiring reintervention or reoperation – 0-2.33%	• Clinical Investigation Data (FDA IDE study) • PMCF study data • Literature search (i.e. literature on the subject devices) • Data generated from complaints/spontaneously reported events and may be underreported (i.e. on the subject devices) • Public vigilance databases (on subject devices)	Migration of the graft material from the intended implantation site is a known risk associated with the use of bone grafts. Whether or not migration leads to a negative clinical impact or the need for reoperation/reintervention is not often specified in studies. In a lot of cases, migration is an incidental finding and patients are asymptomatic. Overall migration is reported with comparators in up to 100% of patients. Migration leading to a negative clinical impact or the need for
	i≡FACTOR Flex FR	Spine		Overall - <0.001% Leading to negative impact/requiring reintervention or reoperation – 0%	• PMCF study data • Data generated from complaints/spontaneously reported events and may be underreported (i.e. on the subject devices)	

Undesirable effect / residual risk	Device	Anatomical location	Time frame	Expected frequency/ quantification	Source	Discussion
					• Public vigilance databases (on subject devices, incidence rate not available from public vigilance database data)	reoperation/reintervention is often not reported with comparators.
	i≡FACTOR Putty	Foot and ankle	Post-operatively; up to 12 months	Overall - 0.011% Leading to negative impact/requiring reintervention or reoperation – not reported	• Data generated from complaints/spontaneously reported events and may be underreported (i.e. on the subject devices)	

Adverse effects:

- Wound complications including hematoma, site drainage, infection and other complications that are possible with any surgery.
- Extrusion or migration of the bone void filler, as is possible with any bone void filler, resulting in pain, neural impingement, physical impairment, irritation or wear of an articulating joint, or loss of function; any of which may require revision surgery.
- Non-union, malunion, or delayed union.
- Loss of reduction.
- Refracture.
- Incomplete, or lack of osseous ingrowth into the bone void, as is possible with any bone void filler.
- Transient hypercalcemia.
- Allergic reaction to components of the i≡FACTOR Bone Graft (i≡FACTOR Putty only).
- Allergic reaction to components of the i≡FACTOR Flex FR including the silk component (i≡FACTOR Flex FR only).

4.2. Warnings and precautions

- i≡FACTOR Bone Graft is not intended to provide load-bearing structural support during the healing process. Rigid fixation techniques are recommended as needed to assure stabilization of the defect in all planes. As with any surgical procedure, care should be exercised in treating individuals with pre-existing conditions that may affect the success of the surgical procedure. This includes, but is not limited to, individuals with bleeding disorders of any etiology, long-term steroidal therapy, immunosuppressive therapy or high dosage radiation therapy.
- Do not use if sterile packaging is opened or damaged. Discard or return damaged packaging and all contents.
- i≡FACTOR Bone Graft is designed for single patient use only. Do not attempt to re-sterilize or re-use. Discard unused contents. Attempting to reuse i≡FACTOR Bone Graft will adversely affect product sterility and physical handling characteristics.
- i≡FACTOR Bone Graft should only be used in surgical procedures where it can be adequately contained at the bony void or defect. Avoid overfilling the bone void or pressurizing the treatment site.
- Inadequate containment of i≡FACTOR Bone Graft could result in product migration from the intended bony defect site. If product migration occurs, clinical outcomes may be compromised by the lack of bone graft material in the appropriate space. Potential patient adverse events caused by inadequate containment and migration of i≡FACTOR Bone Graft could include, but are not

limited to the following: pain, neural impingement, physical impairment, irritation or wear of an articulating joint, or loss of function; any of which may require revision surgery.

- The effect of i≡FACTOR Bone Graft on pregnant or nursing patients has not been evaluated.
- The use of i≡FACTOR Bone Graft when mixed with other bone graft substitute products has not been evaluated; therefore, the effectiveness of i≡FACTOR when used in this manner is unknown.

4.3. Other relevant aspects of safety, including a summary of any field safety corrective action (FSCA including FSN) if applicable

Not applicable. No field safety corrective action or field safety notice have been released for i≡FACTOR Putty or i≡FACTOR Flex FR.

5. Summary of clinical evaluation and post-market clinical follow-up (PMCF)

5.1. Summary of clinical data related to equivalent device, if applicable

Conformity was not endorsed by the NB on the basis of equivalence. There are no equivalent devices to the i≡FACTOR Putty or i≡FACTOR Flex FR.

5.2. Summary of clinical data from conducted investigations of the device before the CE-marking, if applicable

At the time of the edition of this version of the SSCP, there was one premarket clinical study performed with i≡FACTOR Putty in the spine with available data on 165 patients over 2 years follow-up (with some associated publications). There were no premarket clinical studies performed with i≡FACTOR Flex FR. The table below summarises the study on i≡FACTOR Putty.

Fusion was higher with i≡FACTOR Putty compared to autograft at 12 and 24 months. At 12 months, fusion with i≡FACTOR Putty was 88.97% compared to 85.82% with autograft. At 24 months, fusion with i≡FACTOR Putty was 97.3% compared to 94.4% with autograft.

PROMs significantly improved from baseline to 24 months follow-up, with maximum improvement in NDI at 6 months. PROMs were similar between i≡FACTOR Putty and autograft at 12 and 24 months.

TABLE 2: SUMMARY OF PREMARKET CLINICAL STUDIES ON I≡FACTOR PUTTY

Study information	Study details and results
Intended purpose – i≡FACTOR Bone Graft is a bone graft substitute material intended to provide bony ingrowth and fusion in gaps and voids	
Study Identification (ID): FDA IDE study, NCT00310440[1], performed under Medical Device Directive (MDD) Arnold et al 2018 [1], Arnold et al 2016 [2], other publications; Arnold et al 2010 [3], Arnold et al 2016 [4], Arnold et al 2020 [5] Country: 19 sites in USA, 3 sites in Canada **Device: i≡FACTOR Putty** *Other devices/ comparator: autologous bone graft (local autograft)*	**Design:** multi-center, single (patient)-blinded, randomized, controlled trial (6 years follow-up per **PMCF C1.1** described in section 5.3.2). **Objectives:** To investigate efficacy and safety of i≡FACTOR Putty compared with local autograft in single-level anterior cervical discectomy and fusion (ACDF) for cervical radiculopathy. **Methods:** The study participants randomly received either i≡FACTOR (n= 165) or local autograft (n= 154) in a cortical allograft ring implanted into the target vertebral interspace prior to placement of the cervical plate. Patient post-operative follow-up was conducted at six weeks, three months, six months, nine months, 18 months, one and two years. Significance level was set to 0.05. **Primary endpoints:** radiologic fusion, change in of the Overall Neck Disability Index (NDI) score from baseline, neurological success assessed in motor, sensory and reflex domain, complications. Composite endpoint of overall success at 12 months was defined as: Fusion (bridging trabecular bone on X-ray +/- CT), Neurological success (sensory, motor, reflex specific for cervical spine), Neck Disability Index (NDI) improvement of >15 from pre-op, Absence of reoperations and device-related serious AEs. **Secondary endpoints:** mean change in pain at neck Visual Analog Scale (VAS), mean change in pain at arm and shoulder VAS, success rates measured by aggregated modified Odom's Criteria, mean change in the Short Form 36 v2 (SF-36v2) Physical Composite Score (PCS), mean change in the SF-36v2 Mental Health Composite Score (MCS), kyphosis

[1] NCT reference: NCT00310440

Study information	Study details and results
Application: ACDF Study status: study completed Actual study population: i≡FACTOR Putty[2]; 165 patients, 165 levels or joints, 57.76% females, 42.24% males, mean age 47.7±9.8 *Local autograft[2]; 154 patients, 154 levels or joints, 62.5% females, 37.5% males, mean age 45.7±9.4*	**Main subject inclusion criteria:** age between 18 and 70, radiographically determined discogenic origin to include at least one of the following characteristics: degenerated/dark disc on magnetic resonance imaging (MRI), decreased disc height compared to adjacent levels on radiographic film, computed tomography (CT), or MRI, and disc herniation on CT or MRI, radicular symptoms by history and physical exam to include at least one of the following characteristics: Arm/shoulder pain, decreased reflexes, decreased strength, and abnormal sensation, pain level at arm/shoulder >4 on 0-10 VAS OR Pain level at neck >4 on 0-10 VAS, NDI >30, involved disc(s) between C3 and C7, undergoing anterior cervical fusion at a single level, failed to gain adequate relief from at least 6 weeks of adequate non-operative treatment. **Main subject exclusion criteria:** systemic infection such as Autoimmune Deficiency Syndrome (AIDS), Human Immunodeficiency Virus (HIV), and active hepatitis, significant metabolic disease that in the surgeon's opinion might compromise bone growth such as osteoporosis or osteomalacia, taking medication for the prevention of osteoporosis, circulatory, cardiac, or pulmonary problems that could cause excessive surgical risk, active malignancy, nondiscogenic source of symptoms (e.g., tumor, etc.), multiple level symptomatic degenerative disc disease, previous cervical fusion, previous cervical decompression at the same level, acute cervical trauma or instability (i.e., subluxation > 3 mm on flexion/extension radiographic film), undergoing treatment for tumor or boney traumatic injury to the cervical spine, rheumatoid disease of the cervical spine, myelopathy, pregnant or planning to become pregnant in the next 2 years, posterior cervical spine procedure scheduled, more than one level to be operated, has a disease process that would preclude accurate evaluation (e.g., neuromuscular disease, significant psychiatric disease). **Recruitment status:** completed (recruitment 2006-2013) **Overall status**: completed in May 2013 with results **Follow-up:** 2 years follow-up (6 years follow-up per **PMCF 1.1** described in section 5.3.2)

[2] Patient numbers and baseline information based on final study report

Study information	Study details and results
	Targeted study population: 82 patients with i≡FACTOR bone graft (Putty), 82 patients with autologous bone graft **Limitations:** The study involved subjects who met detailed inclusion and exclusion criteria and were willing to participate in a randomized controlled trial. Therefore, patients in clinical practice may differ from the patients enrolled in this study.
Summary of results: The study results showed that i≡FACTOR subjects had similar or superior outcomes compared to autograft subjects in outcomes. Primary analysis of this pivotal clinical trial demonstrated that, at one and two years postoperatively, i≡FACTOR is safe and effective in single-level ACDF for the treatment of symptomatic cervical degenerative disc disease (DDD). **Performance:** Outcomes in subjects treated with i≡FACTOR Putty were similar to those treated with autograft bone in all co-primary end-points**.** Fusion outcomes were non-inferior compared to autograft. All secondary outcome measures significantly improved from baseline values to 2 years follow-up The overall success (a prospectively defined composite end-point consisting of fusion, functional gains, neurological success and absence of complications) was significantly higher in i≡FACTOR Putty patients compared to autograft patients at 12 and 24 months. One year post-surgery 99 out of 144 (68.75%) of i≡FACTOR subjects and 82 out of 144 (56.94%) of autograft subjects were classified as overall success (p=.038). After two years, 81 out of 116 (69.83%) of i≡FACTOR subjects and 71 out of 126 (56.35%) of autograft subjects were classified as overall success (p = 0.03).	

Study information	Study details and results									
	% Fusion		Overall success		PROMs					
	12 months	24 months	12 months	24 months	NDI improvement	Neurological success	Safety success	Odom's criteria	SF-36v2 PCS and SF-36v2 MCS	Mean VAS 24 months
i≡FACTOR Putty	88.97% (p=0.42)	97.3% (p=0.21)	68.75% (99/144 patients) (p=0.038)	69.83% (81/116 patients) (p=0.03)	12 months - 79.43% (p=0.29) 24 months – 76.72% (p=0.18)	12 months - 93.71% (p=0.81) 24 months – 94.87% (p=0.69)	12 months - 97.52% (p=0.30) 24 months – 95.03% (p=0.13)	81.4% in both groups reported good or excellent outcomes	No difference at any time point between groups Mean SF-36v2 PCS – 10.23 (p=0.4507) Mean SF-36v2 MCS – 7.88 (p=0.9872)	Arm pain – 5.43 (p=0.2763) Neck pain – 4.78 (p=0.1652)

Study information		Study details and results								
Autograft	*85.82%*	*94.4%*	*56.94% (82/144 patients)*	*56.35% (71/126 patients)*	*12 months - 74.10%* *24 months – 69.05%*	*12 months - 93.01%* *24 months – 93.70%*	*12 months - 95.39%* *24 months – 90.73%*		Mean SF-36v2 PCS – 10.18 Mean SF-36v2 MCS – 7.53	Arm pain – 4.97 Neck pain – 4.41

Benefit: The available fusion data demonstrate that fusion was non-inferior in comparison to autograft. All secondary outcome measures significantly improved from baseline values to 2 years follow-up. The overall success was significantly higher with i≡FACTOR Putty patients compared to autograft patients at 12 and 24 months.

Safety: Adverse event (AE) rate similar in both groups: 83.64% of i≡FACTOR subjects and 82.47% of autograft subjects had one or more AEs. At 24 months, reoperation was required in 7.45% (12/165) i≡FACTOR Putty patients and 10.53% (16/154) autograft patients. There were 6 (3.73%) subsequent surgeries involving index level in i≡FACTOR Putty patients, and there were 13 (8.44%) autograft subjects with re-operation at the index level.

Device deficiency/replacement: There were no reported i≡FACTOR Putty device deficiencies nor allergic reactions.

5.3. Summary of clinical data from other sources, if applicable

5.3.1. Summary of clinical literature evaluation

5.3.1.1. i≡FACTOR Putty

At the time of the edition of this version of the SSCP, there were 11 studies from the literature on i≡FACTOR Putty used in the spine, including 632 patients and 753 levels or joints (follow-up 6 weeks to 24 months). Findings from the clinical literature provide supporting data on the performance of the i≡FACTOR Putty considering fusion, patient reported outcome measures (PROMs) and incidence of safety issues. The available data demonstrate fusion rates for i≡FACTOR Putty and comparator devices as summarised in Table 3 below.

TABLE 3: I≡FACTOR PUTTY AND COMPARATOR FUSION RATES

Follow-up	i≡FACTOR Putty	Comparators[3]
6 months	80-97.7% [7, 8]	Autograft - 59.09% [7]
12 months	50-97.9% [9, 10, 7, 11, 12, 13]	Autograft (local) - 82.22-100% [7, 9, 11]
		Allograft - 20% [12]
		Allograft and INFUSE - 100% [9]
		Allograft and rhBMP-2 - 100% [9]
		Actifuse - 45% [13]
		Vitoss - 33% [13]
17 months	91% [14]	Not available
18 months	90% [6]	Recombinant Human Bone Morphogenetic Protein-2 (rhBMP-2) - 93.2% [10]
20 months	93.58% [15]	INFUSE, autograft and allograft - 94.4% (data not split per group) [15]
24 months	81-100% [16, 7]	Autograft - 93.33% [7]
26 months	Not available	Demineralized bone matrix (DBM) - 98% [10]

In comparative studies, higher fusion was demonstrated for i≡FACTOR Putty at 6 months compared to autograft [11], significantly higher fusion for i≡FACTOR Putty at 6 months and 12 months compared to autograft [7] and at 12 months compared to allograft [12]. Average time to union with i≡FACTOR Putty was significantly quicker than with rhBMP-2 or DBM at 4.05±2.01 months, with fusion in the first 6 months seen in 89.1% of i≡FACTOR Putty patients [10].

European Quality of Life Five Dimension (EQ-5D) was significantly improved from baseline to 3-, 12- and 24-months follow-up [12]. Data from randomised controlled trials show PROMs were improved from baseline and there were no differences between comparator groups. Overall clinical success

[3] From directly comparative studies

(composite end-point including radiological, PROMs and safety end-points) was greater in patients treated with i≡FACTOR Putty compared to autograft in anterior cervical discectomy and fusion.

Table 4 below summarises the studies from the clinical literature on i≡FACTOR Putty (comparative data are presented in italic).

TABLE 4: CLINICAL LITERATURE ON i≡FACTOR PUTTY

Study	Application	Study design	Follow-up	# Patients	# levels or joints	Spine		Performance		Safety
						Cervical	Lumbar	% Fusion	PROMs	
Berg et al 2014a [8]	Spine: ACDF	Retrospective review	Mean 26 weeks follow-up	17[4]	30		●	Fusion by 26 weeks - 24 levels (80%) Progressing fusion by 17 weeks - 5 levels (17%) No fusion - 1 level (3%)	Not reported.	No AEs associated with the bone graft were reported.
Mobbs et al 2014 [16]	Spine: ALIF	Prospective study	Mean 24 months follow-up (range 15 – 45 months)	110	142		●	Single Level = 97.5% Double Level = 81% Triple level = 100%	Oswestry disability index (ODI), Short form-12 (SF-12), VAS pain at baseline, 3, 6, 12 & 24mth: statistically significant improvement compared to preoperative. Odom's criteria: 85.3% had excellent to good outcomes.	Overall complications rate was 10%. All complications were associated with the surgical exposure and approach. Although graft migration was observed on CT there was no increase in rate of abdominal issues, infection, or retrograde ejaculation.
Mobbs et al 2016 [9]	Spine: ALIF	Retrospective review	12 months	8	8		●	Fusion – 87.5% (7/8 i≡FACTOR patients)	Improvements in ODI, Pain and SF-12 was seen in all patients. Clinical results of the study were not stratified by graft type.	No device related events. No infections. One (1) of the patients who received i≡FACTOR Bone Graft failed to fuse and another had a hernia.

[4] i≡FACTOR Putty combined with local autograft.

Study	Application	Study design	Follow-up	# Patients	# levels or joints	Spine		Performance		Safety
						Cervical	Lumbar	% Fusion	PROMs	
		Vs autograft		*1*	*Not specified (NS)*		●	*Fusion – 100%*		*No device related events. No infections.*
		vs allograft and INFUSE		*9*				*Fusion – 100%*		*No device related events. No infections.* *One (1) of the patients had post-operative hematuria.*
		vs allograft and rhBMP-2		*2*				*Fusion – 100%*		*No device related events. No infections.*

Study	Application	Study design	Follow-up	# Patients	# levels or joints	Spine		Performance		Safety
						Cervical	Lumbar	% Fusion	PROMs	
Rao et al 2015a [14]	Spine: ALIF	Prospective study	17 months	27[5]	32		●	91%	SF-12 Mental Component Summary (MCS) – 31.7 to 43.0 (p = 0.007) SF-12 Physical Component Summary (PCS) – 35.4 to 51.7 (p=0.0026) Mean VAS pain score - 7.6 to 2.2 (p < 0.001) Mean ODI - 56.9 to 17.8% (p < 0.0001) Overall clinical success - 93%	Posterior fixation – 3 patients Recurrent L5 radicular pain three (3) days after L5/S1 ALIF for lower back pain and bilateral L5 radiculopathy – One 72 year old male patient.

[5] i≡FACTOR Putty, Infuse (rhBMP-2) or OP-1 (rhBMP-7).

Study	Application	Study design	Follow-up	# Patients	# levels or joints	Spine		Performance		Safety
						Cervical	Lumbar	% Fusion	PROMs	
Rao et al 2015b [15]	Spine: ALIF	Prospective study	Mean follow-up 20 months	109	109[6]		●	Data not split per group. Overall radiological fusion rate – 118/125 (94.4%) i≡FACTOR Putty – 102/109 (93.58%)[7] Superior radiological outcomes (fusion .90%) were observed in patients with degenerative disk disease (with and without radiculopathy), spondylolisthesis, and failed posterior fusion, whereas in adjacent segment disease, it was 80%.	Data not split per group. Patients with degenerative disc disease (with and without radiculopathy), spondylolisthesis, and scoliosis had the best clinical response to ALIF, with statistically significant improvement in the SF-12, ODI, and VAS. Failed posterior fusion and adjacent segment disease showed statistically significant improvement in all of these clinical outcome scores, although the mean changes in the SF-12 MCS, ODI, and VAS (back pain) were lower.	Data not split per group. Overall complication rate - 10% Postoperative retroperitoneal hematoma - 3 patients, 2 cases required surgical intervention, 1 case resulted in a posttraumatic stress disorder requiring referral to a psychiatrist Retrograde ejaculation - 4 patients (erectile dysfunction in 1 of these patients) Incisional hernia requiring repair - 2 cases Bowel obstruction (with pre-existing diverticulitis) requiring a laparotomy – 1 case
		Vs INFUSE		*9*	*NS*		●			
		Vs autograft		*6*	*NS*					
		Vs allograft		*1*	*NS*					

[6] Number of levels not reported.
[7] Solid fusion was not seen in 7 patients of the whole group, as a worst case all 7 of these patients received i≡FACTOR Putty fusion would have been seen in 102/109 patients (93.58%).

Study	Application	Study design	Follow-up	# Patients	# levels or joints	Spine		Performance		Safety
						Cervical	Lumbar	% Fusion	PROMs	
Rao et al 2017 [6]	Spine: ALIF	Retrospective review	Minimum 6 weeks (except for one patient) up to 18 months	136	136[8]		●	Data not split between groups. Fusion by latest follow-up - 91.2% (n=114/125) (patients with appropriate radiological follow-up, 22 patients without appropriate follow-up) i≡FACTOR Putty fusion – 90%[9] No fusion – 11 patients	Data not split between groups. All PROMs demonstrated improvement, with reduction in VAS and ODI scores and increase in SF-12 scores. VAS pain score - mean 7.1±0.2 to 2.7±0.2 (P<0.0001) ODI - mean 57.8±2.0 to 28.8±1.8 (P<0.0001) SF-12 PCS - 33.2±1.7 to 41.7±0.9 (P<0.0001) SF-12 MCS score - 38.0±1.2 to 48.9±1.0 (P<0.0001)	Data not split between groups. Subsidence - 15 patients (10.2%) 7 being male, each case was of delayed cage subsidence (DCS) >6 weeks postoperatively.
		Vs rhBMP-2		*11*	*11*[8]		●			

[8] Number of levels not reported, some multilevel procedures but not specified between groups.

[9] As a worst case i≡FACTOR Putty fusion would be over 90%.

Study	Application	Study design	Follow-up	# Patients	# levels or joints	Spine		Performance		Safety
						Cervical	Lumbar	% Fusion	PROMs	
Sathe et al 2022 [10]	Spine: ALIF / DLIF	Retrospective review	Mean 11.65±3.57 months	46	≥46[10]		●	Fusion - 97.9% patients Fusion in first 6 months - 89.1% patients Average time-to-union - 4.05±2.01 months (P<0.001)	Average pre-operative VAS-score - 6.93±2.42, which reduced to 1.02±0.80 at the last follow up. Pre-operative ODI scores - 52.7±18.02, which post-operatively reduced to 33.77±15.52 and further to 15.74±8.3 at the last follow-up.	No incidences of infection. Superficial wound complications - 1-patient. Cage subsidence - 21.7%. Grade 1 - 80% Grade 2 – 20%
		rhBMP-2	*Mean 18.34±9.87 months*	*44*	*≥44*		●	*Fusion – 93.2%* *Average time to union - 10±4.28 months*	*Average pre-operative VAS score - 7.14±1.97, which reduced to 1.21±0.96 at last follow-up* *Pre-operative ODI score - 55.4±16.8, which reduced to 39.42±16.47 and further to 17.41±10.45 at last follow-up*	*No incidences of infection.* *Superficial wound complications - 1-patient* *Cage subsidence – 30.2%* *Grade 1 – 72%* *Grade 2 – 28%*

[10] Number of levels not reported.

Study	Application	Study design	Follow-up	# Patients	# levels or joints	Spine		Performance		Safety
						Cervical	Lumbar	% Fusion	PROMs	
		DBM	*Mean 26.2±14.9 months*	*50*	*≥50*		●	*Fusion – 98%* *Average time to union - 9.44±3.49 months*	*Average pre-operative VAS score - 7.01±2.14, which reduced to 0.54±0.70 at last follow-up* *Pre-operative ODI score - 53.56±19.6, reduced to 38.3±15.89 and further to 16.76±9.81 at last follow-up*	*Infection in 3 patients.* *Superficial wound complications – 2 patients* *Cage subsidence – 14%* *Grade 1 – 85.7%* *Grade 2 – 14.3%*
Lauwerys and Raskin 2014 [7]	Spine: PLIF	Prospective study	3, 6, 12 & 24 months	40	59		●	6 months - 97.7% (P<0.01) i≡FACTOR 12 months - 97.8% (P<0.01) i≡FACTOR 24 months - 95.6% i≡FACTOR (not significant)	ODI, VAS pain at baseline, 3, 6, 12 & 24 month - improvement exceeded success criteria at all timepoints compared to baseline. As the patients received both i≡FACTOR and autograft, the improvements in patient reported outcomes cannot be associated with the graft	No wound problems, no infection, no hematoma, no significant radicular pain problem. Device migration was seen in both groups. 4% patients showed moderate levels at 24-month post-op, with none in the control group. The quantity of materials was between 0.01 to 0l.07 cc.
		Vs local autograft (patients acted as their own control)		*40*	*59*		●	*6 months - 59.09% autograft* *12 months - 82.22% autograft* *24 months - 93.33% autograft (not significant)*		

Study	Application	Study design	Follow-up	# Patients	# levels or joints	Spine		Performance		Safety
						Cervical	Lumbar	% Fusion	PROMs	
Park et al 2021 [11]	Spine: PLIF	Retrospective review	12 months	62	93		●	Successful fusion (X-ray) - 91.3% (84/92) (p=0.127). Successful fusion (CT) - 95.6% (87/91) (p=0.034).	Not reported.	Autolysis - 17.6% (16/91) Subsidence rates - 9.99% (9/91) Hollow formation around pedicle screw - 2.2% (2/91)
		Vs local autograft		*76*	*109*		●	*Successful fusion (X-ray) – 84.1% (90/107)* *Successful fusion (CT) – 86.9% (93/107)*		*Autolysis – 14% (15/107)* *Subsidence rates – 11.2% (12/107)* *Hollow formation around pedicle screw – 9.3% (10/107)*

Study	Application	Study design	Follow-up	# Patients	# levels or joints	Spine		Performance		Safety
						Cervical	Lumbar	% Fusion	PROMs	
Jacobsen et al 2020 [12, 12.a][11]	Spine: PLF	Randomized controlled trial (RCT)	3, 12 & 24 months	49[12]	63		●	12 months - 50% (P<0.001)	ODI, EQ-5D, VAS pain at baseline, 3, 12 & 24 month: statistically significant improvement at all timepoints compared to baseline in both groups. No difference between the two groups.	Not reported.
		Vs allograft		*49*	*63*		●	*12 months - 20%*		
Berg et al 2014b [13]	Spine: TLIF	Retrospective review	12 months	28[13]	35		●	12 months - 57%	Not reported.	Not reported.
		vs Actifuse		*10*	*11*		●	*12 months – 45%*		
		Vs Vitoss BA		*6*	*9*			*12 months – 33%*		

[11]NCT reference: NCT01618435 (longer follow-up performed as per PMCF C1.2, see section 5.3.2)

[12] I≡FACTOR Putty mixed with local autograft

[13] I≡FACTOR Putty mixed with morselized local autograft

5.3.1.2. i≡FACTOR Flex FR

At the time of the edition of this version of the SSCP, there were four studies from the literature on i≡FACTOR Flex FR used in the spine (including three investigator-initiated studies with data held on file at Cerapedics (not yet published)). These studies included 115 patients and 189 levels or joints with follow-up ranging from 3 months up to 3 years. Findings from the clinical literature provide supporting data on the performance of the i≡FACTOR Flex FR considering fusion and PROMs. CT examinations at 3 and 6 months demonstrating remodelling of new formed trabecular approaching that of normal bone [18]. The available data demonstrate fusion rates for i≡FACTOR Flex FR and comparator devices as summarised in Table 5 below.

TABLE 5: I≡FACTOR FLEX FR AND COMPARATOR FUSION RATES

Follow-up	i≡FACTOR Flex FR	Comparators[14]
12 months	85.7-100% (McGillion et al 2022[15], Fernandez et al 2022[15])	Autograft/Allograft - 100% (McGillion et al 2022[15])
18 months	100% (McGillion et al 2022[15])	Autograft/Allograft - 100% (McGillion et al 2022[15])
24 months	94-95.8% • Single level – 97% • Two-level – 86% • Three-level – 100% (Fernandez et al 2022[15], Sabitzer et al 2022[15])	Not available
36 months	100% (Fernandez et al 2022[15])	Not available

In the comparative study (McGillion et al 2022[15]), fusion was 100% for i≡FACTOR Flex FR and autologous/allogenic bone grafts at 12 and 18 months. Fusion reached 85.7% at 12 months, 95.8% at 24 months and 100% at 36 months in the Fernandez study (2022[15]) which included patients with complex adult spinal deformity (ASD) undergoing revision. At 12-24 months, overall fusion was 94% with i≡FACTOR Putty and ranged from 86-100% at different levels (Sabitzer et al 2022[15]). PROMs were improved from baseline in patients with complex ASD undergoing revision (Fernandez et al 2022[15]).

Table 6 below summarises the studies from the clinical literature on i≡FACTOR Flex FR (comparative data are presented in italic).

[14] From directly comparative studies
[15] Investigator-initiated study, not yet published (data held on file at Cerapedics)

TABLE 6: CLINICAL LITERATURE ON I≡FACTOR FLEX FR

Study	Application	Study design	Follow-up	# Patients	# levels or joints	Spine		Performance		Safety
						Cervical	Lumbar	% Fusion	PROMs	
McNally et al 2017 [18]	Spine: ACDF	Prospective case series	3 & 6 months	13	20	●		CT examinations demonstrated the remodelling of new formed trabeculae approaches that of normal bone within 6 months in patients treated with i≡FACTOR Flex FR.	Not reported.	Not described.
Fernandez et al 2022[16]	Spine: Revision ASD	Retrospective review	12, 24 and 36 months	28[17]	48[18]		●	Operative levels fused: 12 months – 85.7% (6/7) 24 months – 95.8% (23/24) 36 months – 100% (9/9)	Statistically significant improvements were obtained at 12-months follow-up in VAS, ODI and Scoliosis Research Society-22 (SRS-22) scores[19].	Not described.

[16] Investigator-initiated study, not yet published (data held on file at Cerapedics)
[17] I≡FACTOR Flex FR used in conjunction with autograft
[18] Number of fusion measurements
[19] Number of patients with PROMs data not specified

Study	Application	Study design	Follow-up	# Patients	# levels or joints	Spine		Performance		Safety
						Cervical	Lumbar	% Fusion	PROMs	
McGillion et al 2022[20]	Spine: ASD	Retrospective review	12 & 18 months	10[21]	25[22]		●	Operative levels fused: 12 months – 100% (16/16) 18 months - 100% (9/9)	Not reported.	Not described.
		Vs Autologous / Allogenic bone grafts		*19*	*23*		●	*Operative levels fused:* *12 months - 100% (12/12)* *18 months - 100% (11/11)*	Not reported.	Not described.
Sabitzer et al 2022[20]	Spine: TLIF	Retrospective review	12-24 months	64	96		●	~12-24 months - overall fusion performance was 94%. Single level – 97% (36/37 patients) Two-level – 86% (19/22 patients) Three-level – 100% (5/5 patients)	Not reported.	Not described.

[20] Investigator-initiated study, not yet published (data held on file at Cerapedics)

[21] I≡FACTOR Flex FR used in conjunction with autograft (i-FACTOR Flex FR laying on top of autograft)

[22] Number of fusion measurements

5.3.2. Clinical data derived from post-market clinical follow-up studies

One PMCF study was performed, gathering data from the British Spine Registry (PMCF C3) for both i≡FACTOR Putty and i≡FACTOR Flex FR. As this is a registry study, this data is summarised in section 5.3.3.

5.3.2.1. i≡FACTOR Putty

At the time of the edition of this version of the SSCP, there were two PMCF studies performed with i≡FACTOR Putty in the spine with available data on 149 patients and 106 levels or joints (where specified) (see Table 7). Both of these PMCF studies were long term follow-up of patients originally included in the FDA IDE study (PMCF C1.1, see section 5.2) and in Jacobsen et al 2020 [12] (PMCF C1.2, see section 5.3.1.1). There was one PMCF study performed with i≡FACTOR Putty in the foot and ankle, with available data on 186 patients, including 170 primary procedures and 16 revision procedures at 6- and 12-months follow-up (PMCF C1.4, see Table 7).

In the spine at 6 years follow-up, fusion was higher with i≡FACTOR Putty compared to autograft with non-inferiority demonstrated. The available data demonstrated fusion at 98.6-99% for i≡FACTOR Putty (PMCF C1.1) compared to 97.3-98.2% with autograft at 6 years. At 5 years, fusion was significantly higher with i≡FACTOR Putty at 60% compared to 30% with allograft (PMCF C1.2). This patient population included elderly patients with comorbidities that would be considered difficult to treat.

In the spine, quality of life as measured by EQ-5D was similar between i≡FACTOR Putty and allograft (PMCF C1.2). PROMs were similar between groups except for VAS pain at arm and neck which was significantly improved with i≡FACTOR Putty (PMCF C1.1) at 6 years follow-up. At 5 years follow-up, ODI and back pain were significantly better with i≡FACTOR Putty compared to allograft, although there was no difference in VAS leg pain or QoL (PMCF C1.2).

In the foot and ankle, a high rate of joint fusion was reported with use of i≡FACTOR Putty (PMCF C1.4):

- 6 months
  - Primary group – 75-96%
  - Revisions group – 80-100%[23]
- 12 months
  - Overall fusion rate - 92.3%
  - Primary group – 73-100%
  - Revisions group – 100%[24]

Fusion was similar or higher compared to data reported in the literature with comparators.

[23] Except in the talo-navicular joint (0/1 fused) and the metatarso-phalangeal joint (0/3 fused)
[24] Except in the metatarso-phalangeal joint (0/3 fused)

TABLE 7: SUMMARY OF PMCF STUDIES ON I≡FACTOR PUTTY

Study information	Study details and results
Intended purpose – i≡FACTOR Bone Graft is a bone graft substitute material intended to provide bony ingrowth and fusion in gaps and voids	
PMCF C1.1, NCT00310440[25], performed under MDD Country: United States of America (USA) **Device: i≡FACTOR Putty** *Comparator: Autograft* **Application: ACDF** Study status: study completed Actual study population: i≡FACTOR Putty; 106 patients[26], 106 levels or joints[27], 61 females (57.5%), 45 males (42.5%), mean age 49.8 (range 33-69)	**Title:** Post Approval Study of i≡FACTOR™ in Single-Level Cervical Anterior Discectomy and Fusion (United States (US) Premarket Approval (PMA)) **Design:** Long term (6-year) follow up of prospective, multi-center randomized controlled study comparing of i≡FACTOR Putty vs Autograft in single level ACDF procedure (**2-yr data published in 2018 from FDA IDE study**, see section 5.2) **Objectives:** Demonstration of long-term efficacy and safety of i≡FACTOR Putty in ACDF procedures **Methods:** Radiographic and clinical follow-up **Outcome measures/primary and secondary endpoints:** Segmental fusion, neurological success, NDI, Short Form-36 (SF-36), Odom's criteria, AEs **Subject inclusion criteria:** Participated in prior RCT **Subject exclusion criteria:** None **Recruitment status:** Completed **Overall status**: Completed

[25] NCT reference: NCT00310440

[26] 106 patients included with data on 72 patients available for radiographic analysis, excluded from overall number of patients treated as this is 6-year follow-up data from the FDA IDE study (see section 5.2)

[27] 106 levels included, excluded from overall number of patients treated as this is 6-year follow-up data from the FDA IDE study (see section 5.2)

<table>
<tr><th>Study information</th><th>Study details and results</th></tr>
<tr><td>Autograft; 114 patients[28], 114 levels or joints, 72 females (63.2%), 42 males (36.8%), mean age 46.5 (range 21-66)</td><td>Follow-up: Completed

Targeted study population (If applicable): Follow-up of RCT

Limitations: None reported.</td></tr>
<tr><td colspan="2">Summary of results: The outcomes of this study demonstrated the continued benefit of i≡FACTOR over the lifetime of the device.

Performance: The study met all four pre-defined co-primary endpoints. At this long-term follow-up point, fusion was higher with i≡FACTOR Putty compared to autograft with non-inferiority demonstrated. Both groups reported similar PROMs except for VAS pain at arm and neck which was significantly improved with i≡FACTOR Putty.</td></tr>
</table>

	% Fusion at 6 years	Radiologic fusion	PROMs							
			Odom's criteria	NDI improvement	Neurological success	SF-36v2 PCS	SF-36v2 MCS	VAS pain at arm	VAS pain at neck	Overall responder rate
i≡FACTOR Putty	98.6% (71/72) (non	99% (103/104) (non inferiority P< .0001)	There were no differences in surgical outcomes as measured by	28.56 (non inferiority P< .0001)	95.89% (70/73) (non inferiority P< .001)	11.67 (p=.4609)	15.93	5.89 (p=0.0038)	4.84 (p< .0343)	63.5%

[28] 114 patients included with data on 75 patients available for radiographic analysis

Study information			Study details and results							
	inferiority P< .0001)		Odom's criteria between the two groups.							
Autograft	*97.3% (73/75)*	*98.2% (109/111)*		*29.17*	*93.7% (70/75)*	*10.37*	*14.42*	*4.41*	*3.68*	*53.8%*

Benefit: The available fusion data demonstrate that fusion was higher with i≡FACTOR Putty compared to autograft at 6 years, with non-inferiority demonstrated. PROMs were similar between groups except for VAS pain at arm and neck which was significantly improved with i≡FACTOR Putty.

Safety: The safety profile was similar between groups. The proportion of subjects with any serious AE (SAE) (i≡FACTOR 49.1% and autograft 51.8%) and with any AE (i≡FACTOR 96.2% (102/106) and autograft 97.4% (111/114) was similar between groups. Secondary surgical intervention was reported in 18.9% (20/106) in the i≡FACTOR group and 20.2% (23/114) in the autograft group (p=.866).

Device deficiency/replacement: Not applicable (long-term follow-up of FDA IDE study, see section 5.2).

PMCF C1.2 [17], NCT01618435[29], performed under MDD Country: Denmark **Device: i≡FACTOR Putty[30]**	**Title**: i≡FACTOR® versus allograft in non-instrumented surgical reconstruction in the elderly with spinal stenosis due to degenerative spondylolisthesis **Design**: Long term (5-year) follow-up of prospective, randomized controlled study comparing i≡FACTOR vs allograft in non-instrumented lumbar fusion (follow-up of Jacobsen et al 2020, see section 5.3.1.1) **Objectives**: Assessment of fusion and Patient Reported Outcomes

[29] NCT reference: NCT01618435
[30] i≡FACTOR Putty mixed with local autograft

Study information	Study details and results
Comparator: Allograft bone graft **Application: PLF** Study status: study completed Actual study population: i≡FACTOR Putty; 43 patients, 71% females, mean age 71.3 *Allograft; 40 patients, 80% female, mean age 70.1*	**Methods**: Radiographic and clinical follow-up **Outcome measures/primary and secondary endpoints:** Radiographic assessment of fusion, ODI, post-surgical complications and AEs **Subject inclusion criteria:** Available for follow-up from prior RCT **Subject exclusion criteria:** None **Recruitment status:** Completed **Overall status**: Completed **Follow-up:** Completed **Targeted study population (If applicable)**: Patients from within prior RCT **Limitations:** None reported (investigator-initiated study)
Summary of results: The study demonstrates maintenance of clinical outcomes and acceptable safety profile for the use of i≡FACTOR in challenging non-instrumented fusions in an elderly patient cohort. **Performance:** Sixty percentage in the ABM/P-15 group vs 30% in the allograft group was classified as fused (P = .037). ODI (i≡FACTOR =18.3 vs 27.9, p=0.02) and back pain (i≡FACTOR =22.7 vs 39.0, p=0.015) were statistically significant in favour of the i≡FACTOR group. There were no significant differences in VAS Leg pain (i≡FACTOR = 24.9 vs 33.0, p = 0.231) or quality of life (QoL) as measured by EQ-5D (i≡FACTOR = 0.83 vs 0.78, p=0.251). **Benefit:** The clinical benefit for i≡FACTOR Putty relates to assisting in bone regeneration and union. ODI and back pain were significantly better with i≡FACTOR Putty compared to allograft, although there was no difference in VAS leg pain or QoL at 5 years.	

Study information	Study details and results
Safety: A total of 21 (20.8%) patients underwent reoperation (i≡FACTOR, 9; Allograft, 12) after a minimum of 5-years follow-up. There was no statistical difference between number and cause of reoperations between the two groups. During early post-operative phase, wound complications were seen in 3 study and 6 control patients. As assessed by CT, 2 patients in the i≡FACTOR group showed graft migration. Complications between the groups were similar. **Device deficiency/replacement:** None	
PMCF C1.4, performed under MDD Country: Australia **Device: i≡FACTOR Putty**[31] *Comparator: None, review of and comment on data from literature on comparators in comparison to i≡FACTOR Putty data* **Application: Foot and Ankle** Study status: study completed Actual study population: i≡FACTOR Putty; 186 patients, 236 levels or joints, 170 patients undergoing primary	**Title:** Joint Fusion Rates using i≡FACTOR in Foot and Ankle Surgery – A Retrospective Review **Design:** Retrospective review of patients undergoing foot and ankle surgery in a single centre **Objectives:** This study aimed to investigate joint fusion rates using i≡FACTOR during foot and ankle surgery **Methods**: Patients who underwent joint fusion in the foot and ankle region performed by a single surgeon between June 2016 and August 2020 with i≡FACTOR were evaluated. A single surgeon performed the joint fusions. Types of fusions in the primary group included ankle joint (40 patients, 24%), tarso-metatarsal joint (37 patients, 22%), subtalar joint (35 patients, 21%), tibio-talo-calcaneal (18 patients, 11%), subtalar, talo-navicular joint (13 patients, 8%), naviculo-cuneiform, tarso-metatarsal joint (6 patients, 4%), talo-navicular, naviculo-cuneiform, tarso-metatarsal joint (3 patients, 2%), naviculo-cuneiform joint (2 patients, 1%), talo-navicular, naviculo-cuneiform, calcaneo-cuboid joint (2 patients, 1%), metatarso-phalangeal joint (1 patient, 1%), subtalar, talo-navicular, naviculo-cuneiform, tarso-metatarsal joint (1 patient, 1%), subtalar, metatarso-phalangeal joint (1 patient, 1%), talo-navicular, tarso-metatarsal joint (1 patient, 1%), ankle, subtalar, talo-navicular joint (1 patient, 1%), tarso-metatarsal, metatarso-phalangeal joint (1 patient, 1%), subtalar, talonavicular, metatarso-phalangeal joint (1 patient, 1%), talonavicular, naviculo-cuneiform joint (1 patient,

[31] Calcaneal bone graft was harvested and mixed with i≡FACTOR Putty in approximately 50/50 ratio

Study information	Study details and results
procedures in 218 joints, 16 patients undergoing revision procedures in 18 joints. Primary procedures: gender not specified, mean age 56 Revision procedures: gender not specified, mean age 57	1%). Types of fusions in the revision group included subtalar joint (5 patients, 31%), ankle joint (3 patients, 19%), metatarso-phalangeal joint (3 patients, 19%), tibio-talo-calcaneal (2 patients, 13%), tarso-metatarsal joint (1 patient, 6%), subtalar, talo-navicular joint (1 patient, 6%), ankle, subtalar, talo-navicular joint (1 patient, 6%). **Outcome measures/primary and secondary endpoints:** clinical and radiological fusion, AEs **Subject inclusion criteria:** Patients over the age of 18 **Subject exclusion criteria:** Not specified **Recruitment status:** Completed **Overall status**: Completed **Follow-up:** Completed **Targeted study population (If applicable)**: NA, retrospective review of patients undergoing foot and ankle surgery performed by a single surgeon. **Limitations:** Retrospective design.
Summary of results: In summary, the study reported a high rate of joint fusion using i≡FACTOR in foot and ankle fusions. The range of joints fused was significant and involved regions of the ankle, hindfoot, midfoot and forefoot. The union rates in this study were similar or higher than those in published literature. No graft-related complications were observed; however, 4% of patients experienced non-unions which required further treatment. **Performance**: The overall fusion rate according to radiographic assessment was 92.3% at 12 months. Fusion varied by joint ranging from 75-96% in the primary group at 6 months, and 73-100% at 12 months. In the revisions group, fusion varied by joint ranging from 80-100% at 6 months, except in the talo-navicular joint (0/1 fused) and the metatarso-phalangeal joint (0/3 fused). At 12 months, fusion was 100% except in the metatarso-phalangeal joint (0/3 fused).	

Study information	Study details and results

Group	Follow-up	Ankle	Subtalar	Talo-navicular joint	Calcaneo-cuboid joint	Naviculo-cuneiform joint	Tarso-metatarsal joint	Metatarso-phalangeal joint
Primary group	**6 months**	40/48 (83%)	52/54 (96%)	22/23 (96%)	7/8 (88%)	9/11 (82%)	30/35 (86%)	3/4 (75%)
	12 months	43/48 (90%)	52/54 (96%)	22/23 (96%)	8/8 (100%)	8/11 (73%)	32/35 (91%)	4/4 (100%)
Revisions group	**6 months**	4/5 (80%)	7/8 (88%)	0/1 (0%)	-	-	1/1 (100%)	0/3 (0%)
	12 months	5/5 (100%)	8/8 (100%)	1/1 (100%)	-	-	1/1 (100%)	0/3 (0%)

Benefit: The available fusion data demonstrate that fusion in the foot and ankle was similar or higher than reported in the literature.

Safety: Complications were 21% in the primary group and 31% in the revision group. There was no correlation between complications and patient demographics – i≡FACTOR Putty was not thought to be associated with any complications. All non-unions needed repeat surgery. Non-union rate was comparable to that in the literature (evaluating clinical/radiological union rates) ranging from 5.2-12% with use of various types of bone graft/bone graft substitute (DiGiovanni et al 2013 [19], Krause et al 2011 [20], Krause et al 2016 [21], Daniels et al 2010 [22]).

Study information	Study details and results

	Any complications	Superficial infections	Deep infections	Repeat surgery	Non-union	Pain[32]	Limp[33]	Walking aids[34]
Primary group	35 (21%)	5 (3%)	6 (4%)	29 (17%)	5 (4%)	6 months – 139 (86%) 12 months – 95 (82%)	6 months – 81 (54%) 12 months – 87 (75%)	6 months – 16 (10%) 12 months – 4 (27%)
Revisions group	5 (31%)	1 (6%)	1 (6%)	6 (38%)	0	6 months – 10 (63%) 12 months – 8 (73%)	6 months – 5 (42%) 12 months – 9 (90%)	6 months – 9 (8%) 12 months – 2 (18%)

Device deficiency/replacement: None reported.

[32] Defined as no/mild pain symptoms
[33] Defined as patients walking with a limp (increased percentage of patients limping at 12 months compared to 6 months due to loss of patient follow-up at 12 months)
[34] Defined as patients using a walking stick/crutch/walker

5.3.2.2. **i≡FACTOR Flex FR**

At the time of the edition of this version of the SSCP, there were no PMCF studies performed with i≡FACTOR Flex FR.

5.3.3. Clinical data derived from medical device registries

The British Spine Registry (BSR) was set up by the British Association of Spine Surgeons to monitor the outcomes of spinal procedures, collecting valuable and insightful data, to better understand procedures and techniques and a patient's experience and quality of life. The association makes it possible for manufacturers of devices to request and obtain anonymised clinical data relating to their own devices. Outcome data are limited to Patient Reported Outcomes (VAS pain, ODI and Q-5DL) and AEs only.

Data records were acquired from the BSR in June 2021 (data held on file at Cerapedics, not published). The records of 522 i≡FACTOR Putty patients (681 levels or joints) and 213 i≡FACTOR Flex FR patients (599 levels or joints) were analysed covering the degenerative, cervical and deformity pathways. These records represent approximately 32.1% of the total data available for these pathways, as baseline data were not available for the remainder and therefore, they were not analysable. This reduces to 7.7% at 2-years, due to patients lost to follow-up or low level of reporting. Analysis of PROMs requires within patient comparisons of outcome scores at the follow-up time points, and the changes from baseline to be aggregated within the study population. Consistent follow-up data was limited, PROMs were analysed using a methodology to allow pooling of data from different subjects at the various time points of the follow-up (i.e. the underlying assumption was that outcome scores were objective in nature rather than subjective to each patient). Consequently, patient numbers at the different follow-up time points were different, and the data between follow-up time points was derived from different patients. Using this method of analysis, it was possible to demonstrate Meaningful Clinically Important Differences (MCID(s)) with PROMs for both i≡FACTOR Putty and i≡FACTOR Flex FR. Registry data for i≡FACTOR Putty is provided in Table 8, and for i≡FACTOR Flex FR in Table 9 below. MCID with NDI (cervical), ODI (lumbar), VAS neck and arm pain (cervical)/VAS back and leg pain (lumbar) and HRQoL were demonstrated with i≡FACTOR Putty for the cervical and lumbar pathways at 24 months, and for VAS back and leg pain at 24 months for the deformity pathway. With i≡FACTOR Putty in the deformity pathway, MCID was demonstrated with ODI and HRQoL at 12 months. With i≡FACTOR Flex FR, MCID was seen with NDI (cervical), ODI (lumbar), VAS neck and arm pain (cervical)/VAS back and leg pain (lumbar) and HRQoL for the cervical and lumbar pathways at 24 months. With i≡FACTOR Flex FR, MCID was seen with ODI, VAS back and leg pain and HRQoL for the deformity pathway at 12 months.

TABLE 8: REGISTRY DATA FOR I≡FACTOR PUTTY

Study	Application	Study design	Follow-up	# Patients	# levels or joints	Spine		Performance	Safety
						Cervical	Lumbar	PROMs	
PMCF C3[35]	Spine: Cervical	Registry study	Up to 2 years	129	161	●		MCID of 15 points in NDI over 24 months post-operative follow-up. MCID of 2-point reduction in VAS neck and arm pain over 24 months post-operative follow-up. MCID of 20% improvement in health-related QoL (HRQoL) as measured by EQ-5D L at 12-months. but not demonstrated at 24-month post-operative follow-up.	There were no device related complications or AEs reported within the extracted data.
	Spine: Lumbar			307	405		●	MCID of 15 points in ODI over 24 months post-operative follow-up. MCID of 2-point reduction in VAS back and leg pain over 24 months post-operative follow-up. MCID of 20% improvement in HRQoL as measured by EQ-5D L over 24 months post-operative follow-up.	
	Spine: Deformity[36]			86	115		●	MCID of 15 points in ODI was demonstrated at 12 months post-operative, but not at 24-months post-operative. MCID of 2-point reduction in VAS back and leg pain over 24 months post-operative follow-up. An MCID of 20% improvement in HRQoL was within the standard deviation of the mean, though the mean was lower at 12 months post-operative. Though still an improvement from baseline, this gain was not demonstrated at 24 months post-operative.	

[35] Within the limits to the real-world evidence, the number refer to treated population only. Gaps in data required a reduction in population sample and assumptions to allow analysis of performance. Data includes both interbody and posterior fusion data.
[36] Deformity pathway included long fusions which may include cervical, thoracic and lumbar regions

TABLE 9: REGISTRY DATA FOR I≡FACTOR FLEX FR

Study	Application	Study design	Follow-up	# Patients	# levels or joints	Spine		Performance	Safety
						Cervical	Lumbar	PROMs	
PMCF C3[35]	Spine: Cervical	Registry study	Up to 2 years	46	74	●		MCID of 15 points in NDI over 24 months post-operative follow-up. MCID of 2-point reduction in VAS neck and arm pain over 24 months post-operative follow-up. MCID of 20% improvement in HRQoL as measured by EQ-5D L over 24 months post-operative follow-up.	There were no device related complications or AEs reported within the extracted data.
	Spine: Lumbar			125	186		●	MCID of 15 points in ODI over 24 months post-operative follow-up. MCID of 2- point reduction in VAS back and leg pain over 24 months post-operative follow-up. MCID of 20% improvement in HRQoL as measured by EQ-5D L over 24 months post-operative follow-up.	
	Spine: Deformity [36]			42	339		●	An MCID of 15 points in ODI was demonstrated at 12-month post-operative, but there were inadequate data sets to allow a comparison through to 24 months. MCID of 2-point reduction in VAS back and leg pain over 12 months post-operative, but there were inadequate data sets to allow a comparison through to 24 months. No improvement in leg pain was demonstrated. An MCID of 20% improvement in HRQoL was within the standard deviation of the mean, though the mean was lower at 12 months post-operative. There were inadequate data sets to compute any changes at 24 months post-operative.	

5.4. An overall summary of the clinical performance and safety

Available data on the use of i≡FACTOR Putty in the spine was identified from 15 sources (one premarket study, 11 studies from the literature, two PMCF studies, one PMCF registry study), including 1319 patients and 1599 levels or joints (where specified/applicable), with follow-up ranging from 6 weeks to 6 years. There was one PMCF study performed with i≡FACTOR Putty in the foot and ankle, with available data on 186 patients, including 170 primary procedures and 16 revision procedures at 6- and 12-months follow-up (PMCF C1.4).

Available data on use of i≡FACTOR Flex FR in the spine was identified from five sources (one study from the literature, three unpublished investigator-initiated studies (IIS), one PMCF registry study), including 328 patients and 788 levels or joints, with follow-up ranging from 3 months to 2 years.

The clinical benefit for i≡FACTOR Putty and i≡FACTOR Flex FR relates to assisting in bone regeneration and union, to improve functionality and quality of life. In addition, in certain circumstances, i≡FACTOR Bone Graft renders autologous bone grafting unnecessary.

The available data obtained in the spine demonstrated the following fusion rates summarised in Table 10 below, which supports the clinical benefit for the devices.

TABLE 10: I≡FACTOR PUTTY, I≡FACTOR FLEX FR AND COMPARATOR FUSION DATA

Follow-up	i≡FACTOR Putty	i≡FACTOR Flex FR	Comparators[37]	State of the art
6 months	80-97.7% [FDA IDE study, 7, 8]	Not available	Autograft - 59.09% [7]	Overall - 0-100%
12 months	50-97.9% [9, 10, 7, 11, 12, 13]	85.7-100% (McGillion et al, 2022, Fernandez et al, 2022)	Autograft (local) - 82.22-100% [FDA IDE study, 7, 9, 11]	Overall – 0-100%
			Allograft - 20% [12]	
			Allograft and INFUSE - 100% [9]	
			Allograft and rhBMP-2 - 100% [9]	
			Actifuse - 45% [13]	
			Vitoss - 33% [13]	
			Autograft/Allograft - 100% (McGillion et al, 2022)	
17 months	91% [14]	Not available	Not available	Not reported

[37] From studies comparing i-FACTOR Putty or Flex FR directly to alternatives

Follow-up	i≡FACTOR Putty	i≡FACTOR Flex FR	Comparators[37]	State of the art
18 months	90% [6]	100% (McGillion et al, 2022)	Autograft/Allograft - 100% (McGillion et al, 2022) rhBMP-2 - 93.2% [10]	Overall – 0-100%
20 months	93.58% [15]	Not available	INFUSE, autograft and allograft - 94.4% (data not split per group) [15]	Not reported
24 months	81-100% [FDA IDE study, 16, 7]	94-95.8% • Single level – 97% • Two-level – 86% • Three-level – 100% (Fernandez et al, 2022, Sabitzer et al, 2022)	Autograft - 93.33-94.4% [FDA IDE study, 7]	Overall – 30-100%
26 months	Not available	Not available	DBM - 98% [10]	Not reported
36 months	Not available	100% (Fernandez et al, 2022)	Not available	Overall – 37-100%
5 years	60% (PMCF C1.2)	Not available	Allograft – 30% (PMCF C1.2)	Overall – 97.5-99%
6 years	98.6-99% (PMCF C1.1)	Not available	Autograft - 97.3-98.2% (PMCF C1.1)	Not reported

In the spine, the available clinical data demonstrated that i≡FACTOR Putty and i≡FACTOR Flex FR were both able to produce similar or superior bone growth, as determined by the rate of fusion success relative to other bone graft materials, including autograft and allograft. This is based on data from comparative studies as well as comparing to the general state of the art. Fusion rates with i≡FACTOR Putty at 5 years were significantly higher compared to allograft, although the rates were lower than those reported in the general state of the art. This patient population included elderly patients with comorbidities that would be considered difficult to treat. Fusion data with i≡FACTOR Flex FR at 12, 24 and 36 months from the Fernandez study (2022[15]) was similar or superior to the general state of the art despite including patients with complex ASD undergoing revision. Average time to union with i≡FACTOR Putty was significantly quicker than with rhBMP-2 or demineralized bone matrix (DBM) at 4.05±2.01 months, with fusion in the first 6 months seen in 89.1% of i≡FACTOR Putty patients. With i≡FACTOR Putty, quality of life (measured using EQ-5D) was significantly improved from baseline to 3-, 12- and 24-months follow-up, and was similar compared to allograft. HRQoL demonstrated 20% improvement with i≡FACTOR Putty for the cervical and lumbar pathways at 24 months, and for the deformity pathway at 12 months. With i≡FACTOR Flex FR, HRQoL improved 20% for the cervical and lumbar pathways at 24 months, and for the deformity pathway at 12 months.

i≡FACTOR Putty also demonstrated improvement from baseline as well as similar or superior PROMs when compared to other available bone graft options. Overall clinical success (composite end-point including radiological, PROMs and safety end-points) was greater in patients treated with i≡FACTOR Putty compared to autograft in anterior cervical discectomy and fusion. i≡FACTOR Flex FR demonstrated improvement in PROMs from baseline in patients with complex ASD undergoing revision.

In the foot and ankle, a high rate of joint fusion was reported with use of i≡FACTOR Putty. At 6 months, fusion was 75-96% in primary procedures and 80-100%[38] in revision procedures. At 12 months, overall fusion rate was 92.3%, fusion was 73-100% in primary procedures and 100%[39] in revision procedures. Fusion was similar or higher compared to data reported in the literature with comparators. Achievement of arthrodesis is a strong predictor of favourable clinical outcome [68], therefore this data supports the clinical benefit for i≡FACTOR Putty use in foot and ankle.

The reviewed data sources do not raise any safety concerns related with the use of i≡FACTOR Putty or i≡FACTOR Flex FR. The clinical evaluation has not identified any additional warnings, contraindications or side effects directly associated with the use of i≡FACTOR Putty or i≡FACTOR Flex FR that do not already appear in the product literature and IFU. In addition, PMS data has not identified any trends, or new or previously unrecognized risks associated with the use of the devices. The above findings, combined with design and intended use of the devices, support the safety of i≡FACTOR Putty and i≡FACTOR Flex FR when used as intended.

Observations regarding the product safety and performance are derived from a combination of high-quality prospective studies, retrospective reviews and registry data in a real-world setting. Regardless of the healing environment, all study data highlight the regenerative capacity of i≡FACTOR Putty and i≡FACTOR Flex FR in different areas of the spine, foot and ankle.

5.4.1. Device Lifetime

Pre-clinical testing carried out as per international standards on i≡FACTOR bone grafts validated the device lifetime of 2 years. Data collected from premarket studies, PMCF studies and published in the literature is currently available with up to 2 years follow-up for both i≡FACTOR Putty and i≡FACTOR Flex FR, confirming the stability of the device material. Based on this clinical evidence, i≡FACTOR Putty and i≡FACTOR Flex FR successfully demonstrated clinical safety and performance. Planned PMCF studies will provide data over the lifetime and longer follow-up periods. Any AEs related to the subject device will also be covered by Cerapedics PMS System that continuously monitors product performance and safety by means of customer complaint management, adverse event reporting, literature and clinical database review.

5.4.2. Benefit/risk assessment including acceptability of the benefit-risk ratio

Considering the results presented, and the state of the art established in the medical field of i≡FACTOR bone grafts, it is demonstrated that any risks which might be associated with the use of

[38] Except in the talo-navicular joint (0/1 fused) and the metatarso-phalangeal joint (0/3 fused)
[39] Except in the metatarso-phalangeal joint (0/3 fused)

i≡FACTOR Putty and i≡FACTOR Flex FR are acceptable when weighted against the benefits to the patient. This allows the consideration that the benefit/risk ratio is acceptable for both devices when used as intended, and as long as intended users are appropriately informed about known limitations and risks associated with the device.

Regardless of any robust design, user and/or process mitigation controls taken, inherent risks will always be present due to the procedures in which the i≡FACTOR Putty and i≡FACTOR Flex FR are used. The identified residual risks for both devices are identified in section 4.1. All known risks were mitigated through safety by design, protective measures within the medical device or in the manufacturing process, and information for safety provided to the end users. The benefits associated with the i≡FACTOR Putty and i≡FACTOR Flex FR are aligned with the state of the art.

The clinical evidence described above demonstrate that any possible risks associated with the use of i≡FACTOR Putty and i≡FACTOR Flex FR are outweighed by the benefits to the patient. The side effects and risks associated with this device are adequately described in the labeling and have been reduced to an acceptable level.

5.5. Ongoing or planned post-market clinical follow-up (PMCF)

Post-market clinical follow-up (PMCF) activities will be conducted to evaluate device performance and safety and determine new or previously unidentified risks which may impact the benefit/risk evaluation. The requirement for PMCF is subject to annual review as part of the PMS process and includes a review of changes to the state-of-the-art for bone graft technologies. Table 11 summarizes planned PMCF activities.

TABLE 11: PMCF ACTIVITIES

PMCF Activity	Device	Indication	Details
Literature search	i≡FACTOR Flex FR and i≡FACTOR Putty	NA	An updated literature search will be completed annually. The aim of the literature search is to identify peer-reviewed publications, clinical trials or adverse events relating to the clinical use of i≡FACTOR Putty or i≡FACTOR Flex FR for review and analysis of the safety and performance of the device, identification of side effects and potential misuse or off-label use, and characterize real-world device behaviour and clinical outcomes.
i≡FACTOR Putty in patients undergoing ankle fusion	i≡FACTOR Putty	Foot and ankle	Study design: non-randomised prospective cohort study Sample size: 60 patients Status: not yet started Safety endpoints: adverse events Performance endpoints: radiological fusion
i≡FACTOR Flex FR vs Autograft allograft mix in Correction of Adult Spinal Deformity, NCT05038527	i≡FACTOR Flex FR	Spine: ASD	Investigator: Prof. Gehrchen, University of Copenhagen, Denmark Study Design: randomised Controlled Trial Sample Size: 120 patients per group Status: enrolling Safety endpoints: re-intervention rates, adverse events Performance endpoints: radiological fusion, PROMs, cost-effectiveness
i≡FACTOR Flex FR vs Allograft in Adolescent (skeletally mature) Idiopathic Scoliosis	i≡FACTOR Flex FR	Spine: Idiopathic scoliosis	Investigator: Prof. Helenius, University of Helsinki, Finland Study Design: non-randomised controlled trial Sample Size: 40 patients per group Status: enrolment completed Safety endpoints: adverse events including non-union (related to revisions) and deep infections Performance endpoints: maintenance of scoliosis correction at follow-up

6. Possible Diagnostic or Therapeutic Alternatives

Bone graft biomaterials are widely used in orthopaedic procedures. Alternative bone graft materials include, but are not limited to autologous bone, allograft, DBM, xenografts, growth factors, peptides and synthetic biomaterials (including tricalcium phosphate (TCP), hydroxyapatites (HAs), bioactive glass, and metal scaffolds). The graft materials may also be biphasic or composite.

Autologous Bone Graft

Autologous bone graft, bone obtained from the same individual receiving the graft, has osteoconductive, osteoinductive and osteogenic properties required to promote bone healing and also confers the lowest risk of immunological rejection, making it a valuable adjunct to the treatment of posttraumatic conditions such as fracture, delayed union, non-union and malunion [23]. Risks of autologous bone harvest include local pain, bleeding, hematoma, inflammation, infection, abdominal herniation, peritoneal perforation, prolonged wound drainage, iliac wing fracture, meralgia paresthetica, chronic pain, deformity, hypersensitivity scarring, the need for reoperation and, damage to the donor site [24, 25]. Reported complication rates range from 10-50% for autologous bone graft harvesting from the iliac crest [24]. These risks may be avoided by using local autologous bone; however, this does not address the limited quantity of autograft available. This has stimulated the need for bone graft substitutes.

Allograft

Allogenic bone graft (allograft) transplants bone from one person to another. Allograft derived from cadaveric donors represents an osteoconductive agent, lacking both progenitor cells and growth factors, but serving as a scaffold for bone formation. Allograft bone graft avoids the limitations associated with autograft harvest and provides access to a large volume of bone graft [26]. Allograft is available in multiple forms including powder, strips, bone chips, and cage-type formulations. Structural allografts may be used in load-bearing applications in the treatment of acute fractures and revision traumatic reconstruction surgery. Allografts have limitations, such as the lack of donors, high costs, the need for sterilization, the slow biological incorporate rates and the risk of infectious agent transmission or immune mediated tissue rejection [23, 25]. In addition, the biological performance and graft characteristics are also influenced by storage and sterilisation techniques [27, 28, 29].

DBM

DBM is processed allogeneic bone that has undergone mild acid extraction of the mineralized component to result in decalcification of the bone. The process produces a matrix containing collagen fibers that provide an osteoconductive component combined with osteoinductive protein growth factors (e.g. bone morphogenetic proteins, BMPs) and a host of synergistic proteins [30]. DBM is incorporated into a variety of carriers including gels, putties and prefabricated sheets to enhance delivery, handling and resistance to displacement.

As the efficacy of DBM-based products depends on bone forming proteins conserved in the DBM-base, donor selection, initial screening, processing, sterilization and demineralization of raw bone, as well as the choice of carrier and final processing all affect DBM osteoinductive efficacy and surgical

handling [24]. The concentration of bone forming proteins is inconsistent and varies between products and within batches of the same product [31]. Although DBM materials are routinely used in clinical practice, the majority of commercially available products have been evaluated clinically as a graft extender in combination with autograft. Several additional studies have suggested that DBM-based products may also be employed successfully as autologous bone graft substitutes, especially in the cervical spine; however, the majority of these studies are case series with few comparative studies or randomized controlled trials having been performed [30].

Xenograft

Xenografts are tissue transferred from one species to another. Xenografts avoid the limitations of autograft, are readily available in large volumes and provide excellent bone tissue regeneration in comparison to autologous bone. Further benefits of xenograft over allograft include cost, the elimination of the risk of human blood-borne diseases (e.g. HIV, Hepatitis C) and an abundance of source material. During the purification process all organic components are removed to avoid immunological reactions [32]. In addition, the sintering step of the xenograft processing removes all viral material and genetic material. There are several documented publications about using animals in xenografting such as canine [33], bovine [12,23, 24, 25, 26, 27, 28, 29, 30], porcine [31] and coral graft [32, 34]. Bovine bone xenografts have had organic substances extracted; the remaining structure has similar chemical composition as natural bone, including the surface properties. It has a non-antigenic, natural matrix and is identical to the mineral phase of bone tissue; it has been demonstrated to be highly osteoconductive [35].

Natural porous hydroxyapatite (HA) can be obtained from animal bones or seaweeds. Unlike synthetic HA, xenogeneic HA is the preferred biological material because of its stability concerning resorption [34]. All organic material is removed followed by a chemical treatment or high temperature treatment resulting in a naturally porous material, an interconnecting pore structure similar to human bone and good mechanical properties [32].

Disadvantages of xenograft materials include antigenicity, the potential transmission of zoonoses (e.g. Bovine Spongiform Encephalopathy (BSE)) and the potential for processing to compromise the tissue's biomechanical properties.

Growth Factors

Growth factors are important for regulating bone formation because their regulatory functions include cell adhesion, proliferation and differentiation [35]. The use of different growth factors in bone grafts has been investigated due to their ability to augment the healing process of bony defects treated [26]. However, growth factors have a low biological specificity compared to other bone graft options and are also expensive due to the manufacture process. Consequently, the use of growth factors is often restricted in clinical practice to high-risk patients or revision procedures.

Bone morphogenetic proteins (BMPs) are a group of powerful cytokines and growth factors that are members of the transforming growth factor beta (TGF-β) superfamily that act at cell surface receptors to induce intracellular signaling pathways that induce bone formation and remodeling [26]. Although numerous BMP's have been identified and linked to osteogenic differentiation and bone formation [36], the main growth factors used in clinic are: i) rhBMP-2 (Infuse bone graft,

Medtronic) since 2003 ii), BMP-7 (OP-1 putty, Stryker) from 2003 until 2014 when it was withdrawn from the market, and most recently iii), rhPGDF-BB (Augment bone graft®) since 2015 [37]. Growth factors are made available in high, supraphysiological, concentrations to elicit a biological response and are typically combined with a carrier matrix as all of the molecules are soluble and risk quickly diffusing from the target site, potentially leading to undesirable complications.

The combination of rhBMP-2 on an absorbable collagen sponge (Infuse, Medtronic) has been extensively evaluated in clinical studies with positive fusion outcomes compared to autologous bone in orthopaedic [38] and spinal indications [39,40,41]. However, the use of rhBMP-2 is controversial with high rates of complications documented within the literature including heterotropic ossification, increased infection rates, and the potential link with increased rate of cancer in patients particularly when used in the anterior cervical spine [42, 43, 44, 45, 46, 47].

Peptides

Peptides are short amino-acid sequences which are often copied from active sites in larger protein molecules that can be combined with other carrier materials to elicit a biological effect. These graft materials are readily available, address the limitations of autograft and provide an alternative regenerative strategy compared to growth factors. Clinical issues and complications associated with the use of growth factors are attributed to the high concentrations used to achieve a therapeutic effect. The use of peptides mitigates some of the biological risk associated with the use of protein molecules. By using smaller molecules that are more specific to a particular biological action, bone grafts incorporating peptides offer the potential to retain osteogenic effects by mimicking specific signaling and/or binding actions [48, 49]. The use of peptides also offers potential solutions to issues regarding steric effects, immunogenicity and susceptibility to degradation.

Peptide containing bone grafts have a long clinical history and have been used clinically in dental and maxillofacial [50, 51, 52, 53], orthopaedic [33, 54, 55, 56], and spinal procedures [21, 7, 5, 16, 12, 3].

Synthetics

Synthetic biomaterials include ceramic scaffolds (tricalcium phosphates, hydroxyapatites), bioglass and metal scaffolds. Synthetic scaffolds are primarily osteoconductive in which the composition and morphological characteristics determine the fusion biology and speed of host incorporation. Synthetics overcome the limitations of autograft harvest and are non-toxic and immunogenic, and pose virtually no risk of infection. They are readily available, may be formed into different sizes and shapes, and can be stored for long periods.

Tricalcium Phosphates (TCPs) and hydroxyapatite (HA), or some combination of these materials are the most relevant group of synthetic bone graft substitutes [57]. TCPs usually show morphology very different from natural bone. Resorption time of TCP is relatively short (over several weeks) and can be a disadvantage for continuous volume preservation [58]. In contrast, synthetic HA may resorb over the course of years, a risk mitigated using xenograft HA. Ceramic scaffolds are currently used clinically as a graft extender for orthopaedic and spinal procedures [59].

Bioactive glass is composed of silicate, calcium and phosphorus. These materials are, depending on their porosity, osteoconductive and bioactive, with solubility varying from completely soluble to

non-resorbable. The porosity characteristics can be limited. They may be available in compact or porous forms [34] with a composition that can be changed to influence the biological response. Contact of bioglass with biological fluids release ions which promote processes required for bone regeneration and create an environment hostile for microbial growth [60]. These antimicrobial properties are effective for aerobic and anaerobic bacteria and have been evaluated in the treatment of osteomyelitis [61, 62]. Bioactive glass has been used in craniomaxillofacial bone reconstruction, oral, head and neck surgery, spinal procedures, and in the treatment of bone fractures and tumors [60].

Metals that have a long history of use for the repair of bones include stainless steel, titanium-alloy, cobalt–chromium-based products, aluminum, lead and silver. These materials are osteoconductive scaffolds which overcome the limitations of autograft and maybe used in load bearing applications. Several metals that are also biodegradable, such as magnesium (Mg), iron (Fe), zinc (Zn) and their alloys, are gaining increasing interest for bone tissue scaffolds due to their similar mechanical properties to bone [63]. Alloying each metal with ions such as strontium or calcium can be useful for adapting the mechanical and corrosive properties, as well as be beneficial to bone regeneration [35]. Metal substrates can also be processed to provide morphological similarities to bone [64].

Summary of Clinical Practice Guidelines on how to choose the correct therapeutic option:

Clinical Practice Guidelines as confirmed by Abjornson et al. (2018) [65], urge caution when choosing a bone graft substitute due to the variable levels of clinical data available in support of their use. Classes of product such as bone marrow derivatives, DBM and synthetic scaffolds do not require extensive clinical data to obtain market access in some countries, and as such the body of evidence in support of their performance and safety is generally of low quality. In contrast, advanced biologics (growth factors, peptides) must be supported by high quality data. In practice, off-label use is widespread, and the rhBMP group have been associated with serious adverse events including migration, heterotopic bone formation and potentially, an increased rate of malignancy [65, 66, 67].

Systematic reviews of bone regenerative technologies have highlighted a paucity of high-quality evidence supporting the clinical utility of some bone graft options and suggested evidence classification systems are now being proposed [65]. Independent analysis of the literature has also identified a lack of evidence supporting the use of bone grafts as a viable stand-alone alternative to autologous bone. The meta-analysis also notes that the presentation of performance and safety data relating to bone graft substitutes is not without bias [30].

7. Suggested Profile and Training for Users

Suggested user profile: i≡FACTOR Bone Graft is intended to be used by health care professionals e.g., neurosurgeons, orthopedic surgeons, spine surgeons, operating room staff, and individuals involved in preparation and use of the device.
Suggested training for users: Not applicable. Clinical use and placement of i≡FACTOR Bone Graft should be performed by qualified and trained healthcare professionals.

8. Reference to any harmonised standards and Common Specifications (CS) applied

Harmonized standards applicable to the clinical evaluation of i≡FACTOR Bone Graft product family:

Document Name	Identification / Revision	Applies Fully/Partially	Applicability
Sterilization			
Sterilization of Medical Devices – Requirements for Medical Devices to be Designated "STERILE" Part 1: Requirements for Terminally Sterilized Medical Devices	BS EN 556-1:2001 (+A1:2006)	Full	
Sterilization of Health Care Products – Moist Heat – Part 1 Requirements for the Development, Validation and Routine Control of a Sterilization Process for Medical Devices	ISO 17665-1:2006	Full	
Quality System			
Medical Devices – Quality Management System – Requirements for Regulatory Purposes	BS EN ISO 13485:2016+A11:2021	Partial	Clause 7.5.3 does not apply. Cerapedics does not install or verify the installation of its medical devices, therefore this requirement does not apply. Clause 7.5.4 does not apply. Cerapedics does not perform or verify servicing activities of its medical devices, therefore this requirement does not apply. Clause 7.5.10 does not apply. Cerapedics does not use or control any product or material owned or supplied by a customer. All materials and equipment are provided by Cerapedics or qualified suppliers, therefore this requirement does not apply.

Document Name	Identification / Revision	Applies Fully/Partially	Applicability
Biological Safety			
Biological Evaluation of Medical Devices – Part 3: Tests for Genotoxicity, Carcinogenicity and Reproductive Toxicity	ISO 10993-3:2014	Full	
Biological Evaluation of Medical Devices – Part 11: Tests for Systemic Toxicity	ISO 10993-11:2017	Partial	Full applicability for permanent blood-contacting implantable devices.
Medical Devices Utilizing Animal Tissue and Their Derivatives – Part 3: Validation of the Elimination/Inactivation of Viruses and TSE Agents	ISO 22442-3:2007	Full	

No common specifications have been issued by the European commission, which are applicable for the clinical evaluation of the i≡FACTOR Bone Graft product family.

9. Revision history

SSCP revision number	Date issued	Change Description	Revision validated by the notified body
0	03-Nov-2022	N/A; First release	☒ Yes Validation language: English

10. Bibliography

10.1. Clinical data

i≡FACTOR Putty

1. Arnold, P.M., et al., i-Factor™ Bone Graft vs Autograft in Anterior Cervical Discectomy and Fusion: 2-Year Follow-up of the Randomized Single-Blinded Food and Drug Administration Investigational Device Exemption Study. Neurosurgery, 2018. 83(3): p. 377-384.
2. Arnold, P.M., et al., Efficacy of i-Factor Bone Graft versus Autograft in Anterior Cervical Discectomy and Fusion: Results of the Prospective, Randomized, Single-blinded Food and Drug Administration Investigational Device Exemption Study. Spine (Phila Pa 1976), 2016. 41(13): p. 1075-1083.
3. Arnold, P., M. Fehlings, and R. Sasso, Smoking is a Predictor of Response to ACDF with Instrumentation in Patients with Single-Level DDD. 2010. A408-A408.
4. Arnold, P., et al., Efficacy of i-Factor™ Bone Graft versus Autograft in Anterior Cervical Discectomy and Fusion. SPINE, 2016. 41: p. 1.
5. Arnold, P.M., et al., Two-Year Clinical and Radiological Outcomes in Patients With Diabetes Undergoing Single-Level Anterior Cervical Discectomy and Fusion. Global Spine J, 2020: p. 2192568220914880.
6. Rao, P.J., et al., Subsidence following anterior lumbar interbody fusion (ALIF): a prospective study. J Spine Surg, 2017. 3(2): p. 168-175.
7. Lauweryns, P. and Y. Raskin, Prospective analysis of a new bone graft in lumbar interbody fusion: results of a 2- year prospective clinical and radiological study. Int J Spine Surg, 2015. 9.
8. Berg, A., et al., P-115 Cervical Interbody Fusion Rates with i-FACTOR™ Peptide Enhanced Bone Graft. North Tees and Hartlepool NHS Foundation Trust., 2014.
9. Mobbs, R.J., et al., Anterior Lumbar Interbody Fusion as a Salvage Technique for Pseudarthrosis following Posterior Lumbar Fusion Surgery. Global Spine J, 2016. 6(1): p. 14-20.
10. Sathe, A., Lee, S. H., Kim, S. J., Eun, S. S., Choi, Y. S., Lee, S. M., Seuk, J. W., Lee, Y. S., Shin, S. H., & Bae, J. (2022). Comparative Analysis of ABM/P-15, Bone Morphogenic Protein and Demineralized Bone Matrix after Instrumented Lumbar Interbody Fusion. Journal of Korean Neurosurgical Society, 10.3340/jkns.2021.0296. Advance online publication. https://doi.org/10.3340/jkns.2021.0296
11. Sangman Park, M.D., Yeong ha Jeong, M.D., Byeong Jin Ha, M.D., Beom seok Yoo, M.D., Soo-Heon Kim, M.D., Chang Kyu Lee, M.D., Dong Ah Shin, M.D., Seong Yi, M.D., Yoon Ha, M.D., Keung Nyun Kim, M.D. (2021). Efficacy and Safety of Anorganic Bone Matrix/P-15 in Posterior Lumbar Interbody Fusion. J. of Advanced Spine Surgery Volume 11, Number 2, pp 74~79
12. Jacobsen, M.K., et al., Randomized double blind clinical trial of ABM/P-15 versus allograft in noninstrumented lumbar fusion surgery. Spine J, 2020. 20(5): p. 677-684.
    a. Other publications: Andersen, M., M.K. Jacobsen, and S. Overgaard, Five-year patient reported outcomes ABM/P-15 versus allograft in non-instrumented posterolateral fusion. The Spine Journal 2020. 20(9).
13. Berg, A.J., et al., Lumbar Interbody Fusion Rates with Actifuse, i-FACTOR, and Vitoss BA Synthetic Bone Grafts. Global Spine Journal, 2014. 4(1_suppl): p. s-0034-1376731-s-0034-1376731.

14. Rao, P.J., et al., Stand-alone anterior lumbar interbody fusion for treatment of degenerative spondylolisthesis. J Clin Neurosci, 2015. 22(10): p. 1619-24.
15. Rao, P.J., et al., Outcomes of anterior lumbar interbody fusion surgery based on indication: a prospective study. Neurosurgery, 2015. 76(1): p. 7-23; discussion 23-4.
16. Mobbs, R.J., M. Maharaj, and P.J. Rao, Clinical outcomes and fusion rates following anterior lumbar interbody fusion with bone graft substitute i-FACTOR, an anorganic bone matrix/P-15 composite. J Neurosurg Spine, 2014. 21(6): p. 867-76.
17. Andresen, A. K., Carreon, L. Y., Overgaard, S., Jacobsen, M. K., & Andersen, M. Ø. (2022). Safety and Reoperation Rates in Non-instrumented Lumbar Fusion Surgery: Secondary Report From a Randomized Controlled Trial of ABM/P-15 vs Allograft With Minimum 5 years Follow-Up. Global spine journal, 21925682221090924. Advance online publication. https://doi.org/10.1177/21925682221090924.

i≡FACTOR Flex FR

18. McNally, D., et al., P024 - Quantifying the Quality of Graft Remodelling in Cervical Fusion. Global Spine Journal, 2017(7): p. 200S-201S.

10.2. State of the art

19. DiGiovanni CW, Lin SS, Baumhauer JF, et al. Recombinant human platelet-derived growth factor-BB and beta-tricalcium phosphate (rhPDGF-BB/β-TCP): An alternative to autogenous bone graft. J Bone Jt Surg - Ser A. 2013. doi:10.2106/JBJS.K.01422
20. Krause FG, Windolf M, Bora B, Penner MJ, Wing KJ, Younger ASE. Impact of complications in total ankle replacement and ankle arthrodesis analyzed with a validated outcome measurement. J Bone Jt Surg - Ser A. 2011. doi:10.2106/JBJS.J.00103
21. Krause F, Younger ASE, Baumhauer JF, et al. Clinical outcomes of nonunions of hindfoot and ankle fusions. J Bone Jt Surg - Am Vol. 2016;98(23):2006-2016. doi:10.2106/JBJS.14.00872
22. Daniels T, DiGiovanni C, Lau JTC, Wing K, Alastair Y. Prospective clinical pilot trial in a single cohort group of rhPDGF in foot arthrodeses. Foot Ankle Int. 2010;31(6):473-479. doi:10.3113/FAI.2010.0473
23. Kannan, A., S.N.M. Dodwad, and W.K. Hsu, Biologics in spine arthrodesis. Journal of Spinal Disorders and Techniques, 2015. 28(5): p. 163-170.
24. NaPier, Z., et al., Demineralized Bone Matrix Bone Biology and Clinical Use. Seminars in Spine Surgery, 2016. 28(4): p. 196-216.
25. Iaquinta, M.R., et al., Innovative Biomaterials for Bone Regrowth. Int J Mol Sci, 2019. 20(3).
26. Baldwin, P., et al., Autograft, Allograft, and Bone Graft Substitutes: Clinical Evidence and Indications for Use in the Setting of Orthopaedic Trauma Surgery. J Orthop Trauma, 2019. 33(4): p. 203-213.
27. Folsch, C., et al., Effect of Storage Temperature on Allograft Bone. Transfus Med Hemother, 2012. 39(1): p. 36-40.
28. Bormann, N., et al., In vitro testing of the osteoinductive potential of different bony allograft preparations. Arch Orthop Trauma Surg, 2010. 130(1): p. 143-9.

29. Mejdahl, S., et al., Human bone bank allografts stimulate bone resorption and inhibit proliferation in cultures of human osteoblast-like cells. Acta Orthop Scand, 1998. 69(1): p. 63-8.
30. van der Stok, J., et al., The available evidence on demineralised bone matrix in trauma and orthopaedic surgery: A systematic review. Bone Joint Res, 2017. 6(7): p. 423-432.
31. Bae, H.W., et al., Intervariability and intravariability of bone morphogenetic proteins in commercially available demineralized bone matrix products. Spine (Phila Pa 1976), 2006. 31(12): p. 1299-306; discussion 1307-8.
32. Peric Kacarevic, Z., et al., Purification processes of xenogeneic bone substitutes and their impact on tissue reactions and regeneration. Int J Artif Organs, 2018. 41(11): p. 789-800.
33. Gomar, F., et al., P-15 small peptide bone graft substitute in the treatment of non-unions and delayed union. A pilot clinical trial. Int Orthop, 2007. 31(1): p. 93-9.
34. Kolk, A., et al., Current trends and future perspectives of bone substitute materials - from space holders to innovative biomaterials. J Craniomaxillofac Surg, 2012. 40(8): p. 706-18.
35. Perić Kačarević, Ž., et al., An introduction to bone tissue engineering. The International Journal of Artificial Organs, 2020. 43(2): p. 69-86.
36. Lobb, D.C., B.R. DeGeorge, and A.B. Chhabra, Bone Graft Substitutes: Current Concepts and Future Expectations. Journal of Hand Surgery, 2019. 44(6): p. 497-505.e2.
37. Ho-Shui-Ling, A., et al., Bone regeneration strategies: Engineered scaffolds, bioactive molecules and stem cells current stage and future perspectives. Biomaterials, 2018. 180: p. 143-162.
38. Govender, S., et al., Recombinant human bone morphogenetic protein-2 for treatment of open tibial fractures: a prospective, controlled, randomized study of four hundred and fifty patients. J Bone Joint Surg Am, 2002. 84(12): p. 2123-34.
39. Boden, S.D., et al., Use of recombinant human bone morphogenetic protein-2 to achieve posterolateral lumbar spine fusion in humans: a prospective, randomized clinical pilot trial: 2002 Volvo Award in clinical studies. Spine (Phila Pa 1976), 2002. 27(23): p. 2662-73.
40. Dimar, J.R., 2nd, et al., Clinical and radiographic analysis of an optimized rhBMP-2 formulation as an autograft replacement in posterolateral lumbar spine arthrodesis. J Bone Joint Surg Am, 2009. 91(6): p. 1377-86.
41. Fu, R., et al., Effectiveness and harms of recombinant human bone morphogenetic protein-2 in spine fusion: a systematic review and meta-analysis. Ann Intern Med, 2013. 158(12): p. 890-902.
42. Simmonds, M.C., et al., Safety and effectiveness of recombinant human bone morphogenetic protein-2 for spinal fusion: a meta-analysis of individual-participant data. Ann Intern Med, 2013. 158(12): p. 877-89.
43. Carragee, E.J., et al., Retrograde ejaculation after anterior lumbar interbody fusion using rhBMP-2: a cohort controlled study. Spine J, 2011. 11(6): p. 511-6.
44. Carragee, E.J., E.L. Hurwitz, and B.K. Weiner, A critical review of recombinant human bone morphogenetic protein-2 trials in spinal surgery: emerging safety concerns and lessons learned. Spine J, 2011. 11(6): p. 471-91.
45. Smoljanovic, T., S. Dokuzovic, and I. Bojanic, Osteoinductive bone graft substitutes for lumbar fusion. J Neurosurg Spine, 2010. 13(3): p. 407-9.

46. Smucker, J.D., et al., Increased swelling complications associated with off-label usage of rhBMP-2 in the anterior cervical spine. Spine (Phila Pa 1976), 2006. 31(24): p. 2813-9.
47. Vaidya, R., et al., Complications of anterior cervical discectomy and fusion using recombinant human bone morphogenetic protein-2. Eur Spine J, 2007. 16(8): p. 1257-65.
48. Visser, R., et al., Peptides for bone tissue engineering. J Control Release, 2016. 244(Pt A): p. 122-135.
49. Bullock, G., et al., Osteogenic Peptides and Attachment Methods Determine Tissue Regeneration in Modified Bone Graft Substitutes. J Funct Biomater, 2021. 12(2).
50. Kasaj, A., et al., Clinical evaluation of anorganic bovine-derived hydroxyapatite matrix/cell-binding peptide (P-15) in the treatment of human infrabony defects. Clin Oral Investig, 2008. 12(3): p. 241-7.
51. Yukna, R.A., et al., Multi-center clinical evaluation of combination anorganic bovine-derived hydroxyapatite matrix (ABM)/cell binding peptide (P-15) as a bone replacement graft material in human periodontal osseous defects. 6-month results. J Periodontol, 1998. 69(6): p. 655-63.
52. Yukna, R.A., et al., Multi-center clinical comparison of combination anorganic bovine-derived hydroxyapatite matrix (ABM)/cell binding peptide (P-15) and ABM in human periodontal osseous defects. 6-month results. J Periodontol, 2000. 71(11): p. 1671-9.
53. Barros, R.R., et al., Anorganic bovine matrix/p-15 "flow" in the treatment of periodontal defects: case series with 12 months of follow-up. J Periodontol, 2006. 77(7): p. 1280-7.
54. Ferracini, R., et al., Bone Loss in Distal Radial Fractures Treated with A Composite Xenohybrid Bone Substitute: A Two Years Follow-Up Retrospective Study. Materials (Basel), 2020. 13(18).
55. Conti, A., et al., Femoropatellar Osteoarthritis and Trochlear Femoral Bone Defect due to Giant Cell Tumor of the Knee: A Selected Patellofemoral Joint Arthroplasty and Reconstructive Technique: A Case Report. JBJS Case Connect, 2020. 10(1): p. e0378.
56. Boffano, M., et al., A Preliminary Study on the Mechanical Reliability and Regeneration Capability of Artificial Bone Grafts in Oncologic Cases, With and Without Osteosynthesis. J Clin Med, 2020. 9(5).
57. Kurien, T., R.G. Pearson, and B.E. Scammell, Bone graft substitutes currently available in orthopaedic practice: the evidence for their use. Bone Joint J, 2013. 95-B(5): p. 583-97.
58. Grabowski, G. and C.A. Cornett, Bone graft and bone graft substitutes in spine surgery: current concepts and controversies. J Am Acad Orthop Surg, 2013. 21(1): p. 51-60.
59. Gupta, A., et al., Bone graft substitutes for spine fusion: A brief review. World J Orthop, 2015. 6(6): p. 449-56.
60. Drago, L., M. Toscano, and M. Bottagisio, Recent Evidence on Bioactive Glass Antimicrobial and Antibiofilm Activity: A Mini-Review. Materials (Basel), 2018. 11(2).
61. Aurégan, J.C. and T. Bégué, Bioactive glass for long bone infection: a systematic review. Injury, 2015. 46 Suppl 8: p. S3-7.
62. Drago, L., et al., Bioactive glass BAG-S53P4 for the adjunctive treatment of chronic osteomyelitis of the long bones: an in vitro and prospective clinical study. BMC Infect Dis, 2013. 13: p. 584.
63. Ghosh, D., et al., Biometals in Health and Disease: A Review. World Journal of Pharmaceutical Research, 2016.

64. Cheng, M.-q., et al., A novel open-porous magnesium scaffold with controllable microstructures and properties for bone regeneration. Scientific Reports, 2016. 6(1): p. 24134.
65. Abjornson, C., et al., ISASS Recommendations and Coverage Criteria for Bone Graft Substitutes used in Spinal Surgery. Int J Spine Surg, 2018. 12(6): p. 757-771.
66. Kaiser, M.G., et al., Guideline update for the performance of fusion procedures for degenerative disease of the lumbar spine. Part 16: bone graft extenders and substitutes as an adjunct for lumbar fusion. J Neurosurg Spine, 2014. 21(1): p. 106-32.
67. Wang, J.C., et al., Development of AOSpine BOnE (Bone Osteobiologics and Evidence) Classification. Global Spine J, 2020. 10(7): p. 871-874.
68. Dhall, S.S., et al., Guideline update for the performance of fusion procedures for degenerative disease of the lumbar spine. Part 5: correlation between radiographic outcome and function. J Neurosurg Spine, 2014. 21(1): p. 31-6.

A summary of the safety and clinical performance of the device, intended for patients, is given below.

Summary of Safety and Clinical Performance (SSCP): CR 336
Revision: 0
Effective Date: 03-Nov-2022

Summary of Safety and Clinical Performance (SSCP) Intended for Patients/Lay Persons[40]:

i-FACTOR Putty

i-FACTOR Flex FR

Sponsor:
Cerapedics, Inc.
11025 Dover Street, Suite 1600
Westminster, CO 80021 USA

This Summary of Safety and Clinical Performance (SSCP) is intended to provide public access to an updated summary of the main aspects of the safety and clinical performance of the devices i-FACTOR Putty and i-FACTOR Flex FR. The information presented below is intended for patients or lay persons. A more extensive summary of its safety and clinical performance prepared for healthcare professionals is found in the first part of this document.

Refer to CR 341, revision 0 for Patient SSCP Readability Validation Report of this document.

***Please note:** The SSCP is not intended to give general advice on the treatment of a medical condition. Please contact your healthcare professional in case you have questions about your medical condition or about the use of the device in your situation. This SSCP is not intended to replace an Implant card or the Instructions For Use to provide information on the safe use of the device.*

[40] The summary of safety and clinical performance was written according to the Medical Device Regulation (EU) 2017/745 and the MDCG 2019-9 Rev. 1 Summary of safety and clinical performance A guide for manufacturers and notified bodies (March 2022)

1 Device identification and general information

- **Device(s) trade name**

  i-FACTOR Putty, i-FACTOR Flex FR

  TABLE 12: LIST OF VARIANTS OF THE MEDICAL DEVICE

Product Code	Description
900-010	i-FACTOR® Putty, 1.0 cc
900-025	i-FACTOR® Putty, 2.5 cc
900-050	i-FACTOR® Putty, 5.0 cc
900-100	i-FACTOR® Putty, 10.0 cc
950-012	i-FACTOR® Flex FR, 12 mm
950-025	i-FACTOR® Flex FR, 25 mm
950-050	i-FACTOR® Flex FR, 50 mm
950-100	i-FACTOR® Flex FR, 100 mm

  i-FACTOR Putty and i-FACTOR Flex FR are part of the same device family. The family is called the i-FACTOR Bone Graft(s) or i-FACTOR Bone Graft device(s).

- **Manufacturer; name and address**

  Cerapedics Inc.

  11025 Dover Street, Suite 1600

  Westminster, CO 80021, USA

- **Basic UDI-DI(s)**

  Basic UDI: 0085000168

- **Year when the device (s) was first CE-marked**

  i-FACTOR Putty – 2008

  i-FACTOR Flex FR – 2014

2 Intended use of the device

- **Intended purpose**

  i-FACTOR Putty and i-FACTOR Flex FR are medical devices which are made to support bone growth. They can be described as artificial bone substitute materials (bone grafts). They are used to fill voids or gaps in the bones or joints. The natural bone then grows

into this artificial bone substitute. This helps the voids and gaps join back together.

- **Indications and intended patient groups**

  i-FACTOR Putty

  i-FACTOR Putty is used to fill voids or gaps in the bones of the spine, foot and ankle. These voids or gaps might be caused by changes in the spine, foot and ankle as you get older. They might be caused by injury or accidents. They might also be created during a surgical operation.

  i-FACTOR Flex FR

  i-FACTOR Flex FR is used to fill voids or gaps in the bones of the spine. These voids or gaps might be caused by changes in the spine as you get older. They might be caused by injury or accidents. They might also be created during a surgical operation.

  Intended patient groups

  Both i-FACTOR Putty and i-FACTOR Flex FR are made for adult patients. These patients will be at least 18 years old. These patients will have bones that are mature enough for the devices to be used. The devices can be used in male and female patients. The devices have not been tested on pregnant or breastfeeding patients.

- **Contraindications**

  In the following situations the device should not be used (contraindications):

  - In areas of the body where there is not enough surrounding bone tissue to give support. In areas like this, the doctor may do other things to stabilize the area while it is healing.
  - In case of allergies to ingredients of i-FACTOR Bone Graft (including allergies to silk for the i-FACTOR Flex FR).
  - If an infection is present in the area where the medical device should be placed.
  - If the area where the medical device is placed might be put under lots of impact or stress.
  - If the blood flow towards the operation site is not good enough.
  - In direct contact with joint gaps (the space in the middle of a moving joint).

- In case of extensive defects of the bone.
- In case of any diseases or disorders that affect the healing process of the bone.
- In case your kidneys do not work properly.
- In patients who will not or cannot follow the instructions, for the follow up time after the operation. In patients addicted to drugs and/or alcohol.

3 Device description

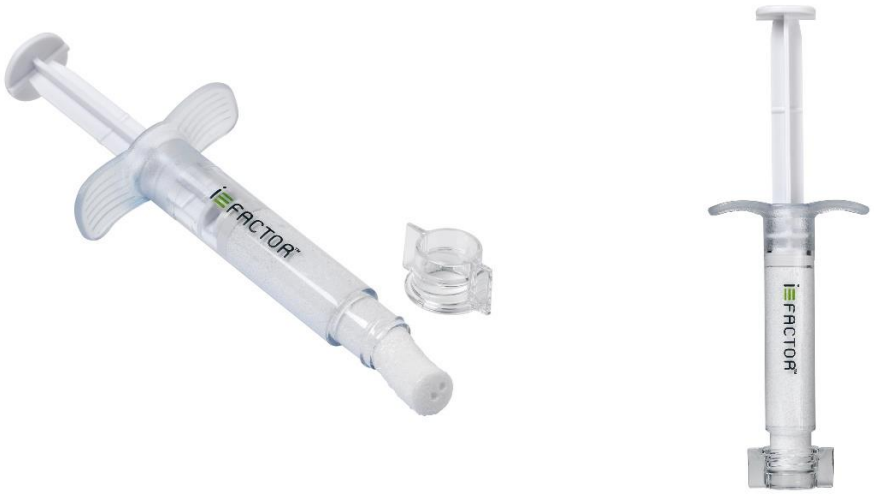
- **Device description (s) and material/substances in contact with patient tissues**

The i-FACTOR Putty and i-FACTOR Flex FR materials are delivered sterile for the operation. They are intended to be used solely in one patient (single use).

i-FACTOR Putty and i-FACTOR Flex FR contain mineral particles, which are like natural bone. They also contain a man-made collagen fragment (called P-15). This is like natural collagen made by the body. This mixture helps your cells bind to the surface of the bone substitute material.

i-FACTOR Putty is a paste that has a putty-like consistency (Figure 2). It can be injected into voids and gaps from a syringe during an operation.

FIGURE 2: I-FACTOR PUTTY.



i-FACTOR Flex FR is made by drying the i-FACTOR Putty material to remove the water. A small amount of purified silk is then added. This means it can be made into dry flexible rectangular strips (Figure 3). The strips give doctors an option for different handling characteristics compared to i-FACTOR Putty paste. The 'FR' acronym in the product name stands for "Fiber Reinforced".

FIGURE 3: I-FACTOR FLEX FR.

- **Information about medicinal substances in the device, if any**

  There are no other medicinal substances in the devices.

- **Description of how the device is achieving its intended mode of action**

  i-FACTOR Putty and i-FACTOR Flex FR are used to fill voids or gaps in the bones or joints. If needed, the voids or gaps will be filled during a surgical operation. At the end of the operation, the doctor closes the wounds. After the operation, the body's own bone in the nearby area grows towards and into the device. The body will absorb the bone graft material. This will then be replaced by the body's own bone. Over time, the voids or gaps are completely closed and filled with natural bone. It is expected that the i-FACTOR Putty and i-FACTOR Flex FR bone graft material will have an effect up to 2 years. Remnants of the bone graft material may remain. This will not cause harm to the body. i-FACTOR Putty and i-FACTOR Flex FR bone graft materials will be visible on imaging scans until they are replaced by natural bone.

- **Description of accessories, if any**

  There are no other devices or products which are intended to be used with i-FACTOR Putty or i-FACTOR Flex FR.

4 Risks and warnings

Important info for patients: Please immediately contact your healthcare professional if you believe that you are experiencing side effects related to the device or its use or if you are concerned about risks. This document is not intended to replace a consultation with your doctor if needed.

- **How potential risks have been controlled or managed**

  Potential risks are controlled and managed by the manufacturer. This is done using a set process. This also follows international standards. This allows the manufacturer to predict device risks. A thorough estimate of what might happen when the devices are used is given. A list of possible harms of the medical devices and what might cause them is created. The Instructions for Use describe warnings, precautions and remaining risks. Immediate actions will be taken by the manufacturer to protect the health of patients if new risks or harms become obvious.

- **Remaining risks and undesirable effects**

  Some risks cannot be completely avoided. These are called remaining (residual) risks. There are also general risks which are linked with an operation. These should be well known by your doctor. They are not described below.

  Undesirable effects linked to these devices can also happen. Patients may experience the typical remaining risks, interactions and undesirable effects after use of the i-FACTOR Putty and i-FACTOR Flex FR. These are described in the sections below.

Remaining risks, that might be linked to the device

TABLE 13: REMAINING RISKS

Remaining Risk	Device	Where in the body	When it might happen	How often it could happen	Discussion
The natural bone doesn't grow into the artificial bone substitute. The voids and gaps don't join back together.	i-FACTOR Putty	Spine	After surgery, between 3 months and 6 years.	Rarely (less than or up to 1 in 10,000 patients) to often (more than 1 in 400 patients).	This is possible with any bone substitute material, or patients own bone. You might need another operation to fix this. i-FACTOR Putty and i-FACTOR Flex FR have shown similar or better rates of bones joining back together, compared to using the patient's own bone.
		Foot and ankle	After surgery, within 12 months.	Rarely (less than 1 in 10,000 patients) to often (more than 1 in 400 patients).	
	i-FACTOR Flex FR	Spine	After surgery, between 3 months and 6 years.	Rarely (less than 1 in 10,000 patients).	
Movement of the material from where it is placed (migration).	i-FACTOR Putty	Spine	During surgery, or after surgery up to 6 years	Rarely (less than 1 in 10,000 patients) to often (more than 1 in 400 patients).	This is possible with any bone substitute material, or patients own bone. This may result in pain, nerve pinching, physical impairment, irritation or wear of a moving joint, or loss of function. Another operation may become necessary. Movement of the material might not cause any issues, even if it does happen. Movement of i-FACTOR Putty or i-FACTOR Flex FR happens at a similar rate compared to other devices.
		Foot and ankle	After surgery, within 12 months.	Rarely (up to 1 in 10,000 patients).	
	i-FACTOR Flex FR	Spine	During surgery, or after surgery up to 6 years.	Rarely (less than 1 in 10,000 patients).	

Adverse effects, that might be linked to the device

- Complications of wound healing. This can happen with any operation. This includes hematoma (a collection of blood under the skin), site drainage, infection and other complications.
- Movement of the material from where it is placed. The material might also be discharged from the operation site. This is possible with any bone substitute material, or patients own bone. This may result in pain, nerve pinching, physical impairment, irritation or wear of a moving joint, or loss of function. Another operation may become necessary.
- A delayed or missing joining of the bone. This is possible with any bone substitute material, or patients own bone.
- Loss of reduction.
- Refracture of the bone.
- The natural bone doesn't grow into the artificial bone substitute. The voids and gaps don't join back together. This is possible with any bone substitute material, or patients own bone.
- Temporary increase in calcium blood levels which may cause muscle weakness.
- Allergies / allergic reaction to components of the i-FACTOR Putty.
- Allergies / allergic reaction to components of the i-FACTOR Flex FR including the silk component.

- **Warnings and precautions**
  - i-FACTOR Putty and i-FACTOR Flex FR should not be placed in areas of the body which are put under heavy load or stress while the area is healing. The area treated should be stable while it is healing. In areas like this, the doctor may do other things to stabilize the area while it is healing.
  - Patients with some specific diseases need to be treated with caution. This is the same with any surgical procedure. This includes patients with bleeding disorders and patients under high dosage radiation therapy. This also includes patients on long-term steroids or therapy that reduces the activity of the immune system.

- The i-FACTOR Putty and i-FACTOR Flex FR materials are delivered sterile for the operation. They are intended to be used solely in one patient (single use).
- The effect of i-FACTOR Bone Graft on pregnant or breastfeeding women has not been tested.
- There is no experience of mixing i-FACTOR Putty and i-FACTOR Flex FR with other bone substitute materials.

- **Summary of any field safety corrective action, (FSCA including FSN) if applicable**

  A so-called “Field Safety Corrective Action” is an action a manufacturer must carry out to reduce a risk of serious health issues. It relates to issues linked with the use of a medical device. It is applied when a problem is found with a medical device in the market. In this case, the manufacturer must tell the medical authorities. The medical authorities will then tell the market by a so-called “Field Safety Notice” (FSN).

  For i-FACTOR Putty and i-FACTOR Flex FR, no FSCAs or FSNs have been carried out.

5 Summary of clinical evaluation and post-market clinical follow-up

- **Clinical background of the device**

  i-FACTOR Putty has been marketed since 2008. i-FACTOR Flex FR has been marketed since 2014. Since then, no changes were made to the devices. The devices have a long clinical track record of safety and performance.

- **The clinical evidence for the CE marking**

  The available clinical evidence is based on clinical data from several studies. These studies were conducted before (Pre-Market study) and after the devices were available to patients. Data was retrieved from literature or actively collected by the manufacturer (Post Market Clinical Follow-up studies). The studies were carried out to make sure the devices are still safe and do what they’re supposed to. In patients with gaps or voids in bones, the aim of using a bone graft substitute material would be to help the bones join. One of the main things the studies looked at was bone joining.

  i-FACTOR Putty in the spine

i-FACTOR Putty device has been the subject of many studies. There were 15 sources of data on use of i-FACTOR Putty in the spine. These studies included 1319 patients. The studies had different follow-up times, from 3 months to 6 years.

The results for bone joining was similar or higher for i-FACTOR Putty compared to other treatments. Joining of bones happened quicker on average (in about 4 months) with i-FACTOR Putty compared to other treatments. Patients noticed improvements after use of i-FACTOR Putty compared to before their surgery. This included an improvement in quality of life. This was mostly similar with use of the alternatives.

The results of these studies support the use of the i-FACTOR Putty in the spine.

i-FACTOR Putty in the foot and ankle

There was one study with i-FACTOR Putty in the foot and ankle. A total of 186 patients were treated with i-FACTOR Putty in this study. Results were collected at 6 and 12 months. Bone joining was similar or higher compared to other treatments.

The results of this study support the use of i-FACTOR Putty in the foot and ankle.

i-FACTOR Flex FR in the spine

There were 5 sources of data for i-FACTOR Flex FR used in the spine. These studies included 328 patients. The studies had different follow up times (3 months to 2 years). New bone was seen in the spine 3 to 6 months after use of i-FACTOR Flex FR. Compared to other treatments, the results for bone joining were similar for i-FACTOR Flex FR. Patients improved after use of the device compared to before their surgery. This included an improvement in quality of life. This was similar with use of the other treatments.

The findings from the studies support the use of the i-FACTOR Flex FR in the spine.

- **Safety**

  i-FACTOR Putty and i-FACTOR Flex FR are medical devices which are made to support bone growth.

  Information is constantly collected on the i-FACTOR Putty and i-FACTOR Flex FR devices. This is to make sure they are still safe and doing what they’re supposed to do. Lots of different sources of information are included. The manufacturer conducts clinical studies to constantly make sure the devices are still safe. There are publicly available databases which have reports of any safety issues. These databases are regularly searched to see if there are any safety issues with the

devices. The manufacturer also collects data from complaints. Complaints may come from doctors that use the device. All this data is reviewed on a regular basis.

This information is used to make sure the benefits of i-FACTOR Putty and i-FACTOR Flex FR for patients always outweigh the possible risks. Some safety issues are to be expected. The manufacturer has reliable procedures in place to make sure patients and healthcare professionals know of any safety issues in a timely manner.

The manufacturer conducts Post Market Clinical Follow-Up (PMCF) studies. These are summarized in **Table 14**. They are done to make sure the devices are safe and do what they're supposed to over a long period of time.

The manufacturer has done everything possible to reduce the risks with the devices. There are no new safety concerns or risks with the use of the i-FACTOR Putty or i-FACTOR Flex FR.

- **Ongoing Safety and PMCF**

  Table 14 below describes the overview of PMCF on i-FACTOR Putty and i-FACTOR Flex FR.

Table 14: Overview of PMCF studies on i-FACTOR Putty and i-FACTOR Flex FR

Study details	Key outcomes	Product	Study purpose
A literature search will be done every year.	Key outcomes: - Find any new literature on the devices. - Find any new studies on the devices. - Performance data on the devices. - Any safety issues. - If the devices are being used for procedures they shouldn't be.	i-FACTOR Flex FR and i-FACTOR Putty.	To make sure the devices are still safe and doing what they're supposed to do. Find any new risks.
Patients that need joining of bone in the ankle will be included. Patients will be treated with the device in the ankle joints. The manufacturer is aiming to include 60 patients.	Key outcomes: - Joining of the bone. - Any safety issues.	i-FACTOR Putty.	To make sure the devices are still safe and doing what they're supposed to do.
Patients with adult spinal deformity will be included. Patients will be randomly assigned to use of the device or bone from another person. The manufacturer is aiming to include 120 patients in each group.	Key outcomes: - Joining of the bone. - If the patient has improved. - The need for any more operations. - Any safety issues.	i-FACTOR Flex FR.	To make sure the devices are still safe and doing what they're supposed to do.
Patients with a curve in the spine (idiopathic scoliosis). These patients will have bones that are mature enough for the device to be used. Patients will be treated with the device or bone from another person. The manufacturer is aiming to have 40 patients in each group.	Key outcomes: - The need for any more operations. - If the curve in the spine has been fixed. - Any safety issues.	i-FACTOR Flex FR.	To make sure the devices are still safe and doing what they're supposed to do.

6 Possible diagnostic or therapeutic alternatives

When considering alternative treatments, it is recommended to contact your healthcare professional. They can take into account your individual situation.

i-FACTOR Putty and i-FACTOR Flex FR are medical devices which are made to support bone growth. They can be described as artificial bone substitute materials (bone grafts). They are used to fill voids or gaps in the bones or joints. The natural bone then grows into this artificial bone substitute. This helps the voids and gaps join back together.

The available alternatives come in different materials. These materials are used to fill voids and gaps in the bones or joints. They may also "encourage" the bone to grow into the gaps. Please talk to your doctor about advantages and disadvantages of the different alternatives.

- **Bone from your own body (autologous bone graft)**
  Bone that is taken from one part of your body and placed into a different part of your body to help bone healing. The bone needs to be "harvested" or taken from another body region. This will leave a gap in the bone there. This is not harmful.
- **Bone from another person (allograft)**
  Bone that is taken from another person. The bone is taken from a donor and treated before use (sterilized) to avoid transmission of disease.
- **Bone from another person that is treated (demineralized bone matrix)**
  This bone is taken from another person (as the bone substitute material before). It then undergoes treatments before being used. This extracts the mineral compound of the bone.
- **Non-human bone from another species (xenograft)**
  The bone-like substance is taken from another species. This can be animals or even seaweeds. Seaweeds contain specific mineral structures (called hydroxyapatite), which are similar to human bone mineral.
- **Growth Factors (proteins)**
  Growth factors are proteins (large complex amino acid sequences). They can "encourage" cells to attach to the bone structure in the damaged areas. As such, they improve the bone healing of bone gaps and voids.
- **Peptides (protein fragments)**
  Peptides are small pieces of proteins (short amino acid sequences). They are very similar to Growth Factors in their ability to "encourage" bone growth, but have a more specific action on the body.
- **Synthetics (synthetic bone graft substitutes)**
  The synthetic bone replacement biomaterials are not from animals or humans. They are produced and are based on things like ceramic-like structures. They are composed of minerals, which are well accepted by the human body. These include Tricalcium Phosphates and Hydroxyapatite.

7 Revision History, Data Sources and Release

Revision History			
SSCP rev. number	**Date issued**	**Change description**	**Information**
0	03-Nov-2022	Initial Release	☒ sent to NB: Date 03-Nov-2022 ☒ Validated language of the master SSCP: English ☐ Other validated languages: ☒ Readability validation ☐ No (only applicable for class IIa or some class IIb implantable devices (MDR, Article 52 (4) 2nd paragraph) for which the SSCP is not yet validated by the NB)