CLINICAL STUDY PROTOCOL

Title: Total Knee Arthroplasty with Vitamin E Polyethylene

Short Title: VITALECOQ2020

ClinicalTrials.gov ID: NCT05810285

Document date	Version	Document history	Ethics Committee approval date
September 18, 2020	01	First protocol release	June 11, 2021
February 9, 2023	02	Substantial amendment for principal investigator change	April 14, 2023

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1. Synopsis

Study title:	Total knee arthroplasty with vitamin E polyethylene.
Protocol ID:	VITALECOQ2020
Protocol versions and dates:	Version number 01 released on 09/18/2020 Version number 02 released on 02/09/2023
Study design:	Single-centre comparative cross-sectional observational clinical study with medical device.
Promoter/Sponsor:	Permedica S.p.A., Via Como 38, 23807 Merate (LC), Italy. https://www.permedica.it/
Study center:	Quadrante Orthopedic Center (C.O.Q.), Lungolago Buozzi 25, 28887 Omegna (VB), Italy.
Principal investigator (Responsible):	Marco Spezia - Head of Surgical Unit and Director of the C.O.Q. Orthopedic Unit, Omegna, Italy (Danilo Mellano - Head of Surgical Unit and Director of the C.O.Q. Orthopedic Unit, Omegna, Italy, after study substantial amendment)
Co-investigators:	• Alessandro Masse' - Director of the Complex Structure Unit 1 Orthopaedics and Traumatology, Città della Salute Hospital / CTO of Turin, Italy. • Alessandro Bistolfi - 1st level Medical Director of Unit 1 Orthopaedics and Traumatology, Città della Salute Hospital/CTO of Turin, Italy and Cardinal Massaia Hospital, Asti, Italy.
Sponsor contact person:	Lorenzo Banci – Clinical Research Manager at Permedica S.p.A.
Study rationale	The clinical evidence for outcomes after primary total knee arthroplasty with vitamin E polyethylene is still scarce in the short term and published clinical studies on vitamin E polyethylene total knee arthroplasty with medium term results are lacking.
Objective	The aim of the study is to investigate on the survival rate and mid-term clinical and radiographic results of a consecutive series of primary total knee arthroplasty performed using a cemented total knee prosthesis with a mobile insert in polyethylene with vitamin E, comparing them with the same implant with a mobile insert in conventional polyethylene.

Primary endpoint	Cumulative implant survival with revision for aseptic loosening as the end-point.
Secondary end-points	Cumulative implant survival with revision for any reason as the end-point. Reinterventions and non-surgical complications Forgotten Joint Score (FJS-12). America Knee Society Score (Knee / Function). Radiographic signs of radiolucencies and osteolysis.
Study group	Minimum 152 total knee arthroplasties with vitamin E polyethylene insert.
Control group	Minimum 152 total knee arthroplasties with the same implant but with conventional polyethylene insert without vitamin E.
Medical device	GKS Prime Flex Mobile Bioloy, cemented TiNbN-coated mobile bearing knee prosthesis by Permedica with vitamin E polyethylene (VitalE®) or conventional polyethylene rotating ultra-congruent tibial insert.
Inclusion criteria	• Patient who received primary total knee arthroplasty with GKS Prime Flex Mobile Bioloy by Permedica with vitamin E polyethylene or conventional polyethylene insert. • Minimum follow-up of 7 years. • Patient aged ≥ 18 years and < 85 years. • Patients who signed the informed consent.
Exclusion criteria	• Patient who received knee prosthesis different from Permedica's GKS Prime Flex Mobile Bioloy. • Patients already included in other clinical investigations. • Patients who do not sign the informed consent.
Telephone contact	Telephone contact of all eligible patients for recording FJS-12, any adverse events, if lost to follow-up or deceased and for scheduling the follow-up visit.
Follow-up visit	Physical examination, AKSS compilation, FJS-12, recording of complications, adverse events, radiographic assessment for periprosthetic radiolucent lines and osteolysis.

2. Introduction and state of the art

One of the most limiting factors for the longevity of a prosthetic implant in hip and knee arthroplasty is the resistance to wear and degradation of the polyethylene acetabular inserts.
The degradation of ultra-high molecular weight polyethylene (UHMWPE) is that process whereby there is an alteration of the chemical structure of the material with a decrease in the molecular weight. Degradation decreases the mechanical characteristics of the polyethylene and, therefore, potentially reduces the longevity of the polyethylene joint insert. Degradation occurs when the polymeric material is exposed to a quantity of energy greater than that of the chemical bonds of which the polymer chains are made up, so that some chemical bonds are broken. and new free radicals are created. This process in the presence of oxygen is called oxidative degradation or more simply oxidation. Once triggered, the oxidative process is irreversible and self-sustaining with the formation of new radicals that react with oxygen, thus creating a chain reaction.

In orthopaedics, polyethylene acetabular inserts are typically subjected to high doses of energy in the form of irradiation with the aim of increasing the degree of cross-linking or sterilizing the device. This radiation, through the splitting of bonds within the polymer chains, produces the formation of active free radicals within the material. Most free radicals recombine, forming new bonds in the amorphous phase of polyethylene, i.e. cross-linking. The free radicals formed inside the crystalline phase remain trapped for a long time and are responsible for oxidation [1-3].

Stabilization with vitamin E

A solution to the problem of oxidative degradation is the addition of doping substances stabilizing against free radicals to UHMWPE. Stabilization of UHMWPE by the addition of vitamin E was introduced in 2005-2006 as an alternative method to annealing and re-melting, to provide greater resistance to oxidation without sacrificing the mechanical properties of UHMWPE. Vitamin E (alpha-Tocopherol) is in fact a natural molecule and is also present in our metabolism as an antioxidant agent. Vitamin E in its synthetic form is added in low concentrations to UHMWPE as a stabilizing agent against oxidative degradation.

Vitamin E would have the advantage of maintaining the chemical and physical properties of the starting raw material over time, therefore prolonging the longevity of the joint component by reducing the risk of breakage, delamination and wear, a risk that increases exponentially with the increase in the degree of oxidation.
The addition of low concentrations of Vitamin E has proven effective in protecting UHMWPE from oxidation in vitro. From research [4,5] it has been seen that a concentration of 0.05% by weight of vitamin E is already sufficient to protect UHMWPE from oxidation.

UHMWPE with vitamin E added represents the latest generation of polyethylene for joint components, developed and introduced on the market in 2006 by Biomet, now Zimmer-Biomet (E1®). Polyethylene added with Vitamin E have recently been regulated through the ASTM F2695-07 standard. On the market today there are many UHMWPEs added with vitamin E which however differ in the treatments they receive during the production process (Table 1).

Commercial name	Raw material	Additive method	Irradiation dose	Irradiation method	Sterilization method
E1™ (Biomet)	GUR 1020/1050	Infused	100 kGy	γ-Beam	γ-Beam
Vitamys® (Mathys)	GUR 1020	Blended	100 kGy	γ-Beam	Plasma gas
Vivacit-E® (Zimmer)	GUR 1020	Blended	100 kGy	E-Beam	Eto
Vitelene® (Aesculap)	GUR 1020	Blended	80 kGy	E-Beam	Eto
Vital-XE® (Permedica)	GUR 1020	Blended	60 kGy	E-Beam	Eto
ECiMa™ (Corin)	na	Blended	120 kGy	Cold E-Beam	na
E-MAX™ (Renovis)	GUR 1020	Blended	100 kGy	γ-Beam	Eto

Table 1. Some of vitamin E-stabilized polyethylene brands for articular inserts for joint replacement in 2018.

Vitamin E UHMWPE in the hip

Numerous clinical studies are reported in the literature regarding primary total hip replacement with cross-linked polyethylene inserts added with vitamin E and the most recent ones show results up to 7 years of follow-up [6,7]. All studies report low linear wear, lower than conventional UHMWPE inserts and comparable to HXPE, and above all they show no signs of periprosthetic osteolysis.

Vitamin E UHMWPE in the knee

Numerous preclinical studies have shown the effective efficacy and safety of adding vitamin E to the polyethylene of joint inserts in total knee arthroplasty [8-11].
Simulator wear tests have shown excellent results with polyethylene inserts added with vitamin E [12-14].

However, in the literature there are few clinical studies published on total knee arthroplasty with polyethylene added with vitamin E and all concern short-term follow-up (maximum 3 years) and cross-linked polyethylene, infused with vitamin E by Zimmer Biomet (E1®), Table 2. To date, the 2 retrospective case series studies confirm comparable short-term clinical, radiographic and survival results of prostheses with inserts with vitamin E compared to inserts without vitamin E [15,16]. A study on retrieved implants after an average in vivo period of 1.5 years reported less damage and less signs of wear and lower level of oxidation on Zimmer Biomet E1 inserts [17].

Ref.	Study design	No. cases	FU	Vit. E insert	Prosthetics	Main outcomes	Conclusion
Takemura, 2019 [15]	Comparative retrospective	100 + 100	2	E1 PS Biomet	VanguardPS cemented	ROM, KSS, radiological signs	No differences
Spece 2019 [17]	Retrievals	103 + 63	1.5	E1 PS vs Arcom PS	VanguardPS cemented	Signs of wear, oxidation	Less oxidation in PE with vit. E
Flament 2016 [16]	Case series	163	3.2	E1	Vanguard cemented	Survival, ROM, KSS, radiological signs	95% survival for any reason
Barrack 2013 [18]	Case report	1	2.5	E1	Vanguard CR casehardened	Insert breakage	No oxidation

Table 2. Literature review on total knee arthroplasty with vitamin E stabilized polyethylene. FU, mean follow-up in years.

Study rationale

The international scientific literature is still lacking in clinical studies reporting the safety, performance and effectiveness of the use of polyethylene added with vitamin E in joint inserts in primary total knee arthroplasty. There is therefore still no short-term clinical evidence on the clinical and radiographic results of these prosthetic implants.

Furthermore, nothing has yet been published in the literature on mid-term results in primary total knee arthroplasty with polyethylene insert added with vitamin E. The maximum follow-up reported from clinical studies in total knee arthroplasty is in fact 3 years.

A study that reports the medium-term results of a series of total knee arthroplasties using polyethylene with vitamin E and comparing them with those of an identical insert but made of conventional polyethylene is therefore considered scientifically valid and well-founded.

The present study therefore aims to verify the survival, clinical and radiographic results of a consecutive series of patients undergoing first-time total knee arthroplasty with a polyethylene insert added with vitamin E, comparing them with an identical insert but made of polyethylene. standard, at a minimum follow-up of 7 years.

3. Study design

Observational, cross-sectional, comparative, monocentric clinical study with a retrospective cohort. The study is promoted and sponsored by Permedica S.p.A., Via Como 38, 23807 Merate (LC), Italy https://www.permedica.it/. The study centre is the Quadrante Orthopaedics Center (C.O.Q.) Hospital, placed in Lungolago Buozzi 25, 28887 Omegna (VB) - Italy. Study principal investigator (PI) will be Dr Marco Spezia. The study will be conducted by PI and other co-investigators, PI's collaborators of the Orthopaedics Unit at C.O.Q. Hospital in Omegna and external collaborators of the CTO Hospital of Turin, coordinated by Prof. Alessandro Massè, Director of the Orthopaedics Unit and Traumatology 1, CTO Hospital of Turin. The study, being observational, will only concern

the collection of data about the patient, his medical history and pathology, his surgery and prosthetic implant and the clinical and radiographic results. The patient will be contacted by telephone and invited to a follow-up visit. Clinical scores will be recorded by the patient and the investigators, radiographic signs will be recorded from preoperative and postoperative radiographs performed at the last follow-up. The study will therefore not require any additional diagnostic or therapeutic services compared to the standard clinical practice. The study will only take into consideration patients who have already undergone total knee arthroplasty at the C.O.Q. Orthopaedics Unit.

4. Study objective

The aim of the study is to verify the survival and mid-longterm clinical and radiographic results of a consecutive series of primary total knee arthroplasty performed using a cemented total knee prosthesis with a vitamin E polyethylene ultra-congruent mobile insert, in comparison to the same implant with a conventional polyethylene same design tibial insert.

4.1 Primary endpoint

The primary objective of the study is to verify that the survival of the prosthetic implant with vitamin E polyethylene is not inferior to the survival of the prosthetic implant with conventional polyethylene. The primary endpoint is therefore the cumulative implant survival, defining revision for aseptic loosening as the endpoint (or failure).

4.2 Secondary endpoints

The secondary objectives of the study are survival for any reason, clinical results and radiographic results, prevalence of complications. Secondary endpoints are therefore:

- Survival of the prosthetic implant with vitamin E polyethylene and with conventional polyethylene, with revision for any reason as the end-point,
- the American Knee Society Score (KSS) with Knee score and Function score,
- the Forgotten Joint Score (FKS-12),
- Number of reinterventions (without any component removal), non-surgical complications and adverse events,
- Periprosthetic radiolucent lines and radiographic signs of periprosthetic osteolysis.

5. Prosthetic device

The medical device under investigation is a cemented bicompartmental knee prosthesis with a rotating tibial plateau, the GKS Prime Flex Mobile Bioloy® by Permedica S.p.A. (Figure 1). The femoral and tibial components are both coated with a titanium-niobium nitride (TiNbN) ceramic coating with 4.5 ± 1.5 microns thickness (Bioloy®). The femoral and tibial component are both cemented. The rotating tibial insert has an ultra-congruent articular surface and is made with

UHMWPE blended with vitamin E (0.1% alpha-Tocopherol), non-cross-linked and sterilized by ethylene oxide (VitalE®), or with conventional non-cross-linked UHMWPE (Figure 2).

Figure 1. Cemented mobile-bearing total knee prosthesis with TiNbN coating, GKS Prime Flex Mobile Bioloy® by Permedica S.p.A.

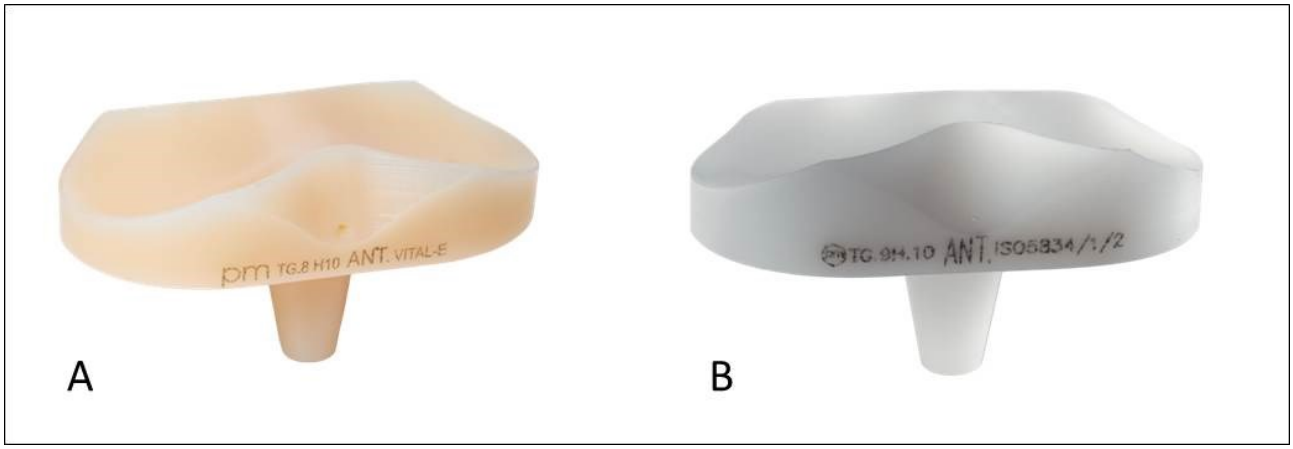

Figure 2. A: UHMWPE blended with 0.1% vitamin E, non-cross-linked and ethylene oxide sterilized (VitalE®) ultra-congruent rotating insert. B: Conventional, non-cross-linked, E-beam sterilized UHMWPE ultra-congruent rotating insert with same desing.

6. Study population

The study will concern a consecutive series of patients who underwent primary total knee arthroplasty with the same knee prosthesis at the C.O.Q. hospital in Omegna (VB), Italy, from January 2011 to December 2015 and who will meet all eligibility criteria.

6.1 Study group

At least 152 knees with GKS Prime Flex Mobile Bioloy prosthesis from Permedica with rotating mobile insert with vitamin E polyethylene (VitalE®).

6.2 Control group

At least 152 knees with Permedica GKS Prime Flex Mobile Bioloy prosthesis with rotating mobile insert with conventional polyethylene without vitamin E.

6.3 Eligibility criteria

Inclusion criteria:

- Patient underwent primary implant total knee arthroplasty surgery cemented with GKS Prime Flex Mobile Bioloy prosthesis with mobile insert by Permedica.
- Patient with minimum follow-up of 7 years.
- Patient aged ≥ 18 years and < 85 years.
- Patients who signed the informed consent.

Exclusion criteria:

- Patient with knee prosthesis other than Permedica's GKS Prime Flex Mobile Bioloy.
- Patients already included in other clinical investigations.
- Patients who do not sign the informed consent.

7. Study procedure

The study can start only upon the approval of this protocol by the competent Ethics Committee of the study centre and after formal communication of the study centre.

7.1 Screening

All patients who underwent primary total knee arthroplasty from January 2011 to December 2015 at the Orthopaedics Unit of the C.O.Q. Hospital in Omegna will be identified through hospital database. If deemed eligible according to the inclusion/exclusion criteria, patients will be contacted by telephone by the principal investigator or one of his representatives and invited to take part in the study. If possible, the patient information sheet, the patient's informed consent form and the information on the processing of personal data will be sent by ordinary post or e-mail. The investigator will invite each patient eligible for the study to present themselves at the C.O.Q. Orthopaedics Unit for a follow-up and will be invited to present themselves with all the radiographic documentation in their possession.

7.2 Enrolment

The principal investigator, or one of his representatives, will explain to the patient the reasons and methods for carrying out the study and provide all the necessary information before enrolment. The patient will be given the Patient Informed Consent form, the Consent to the Processing of Personal Data form. Furthermore, the investigator will be available to provide an adequate response to any questions or concerns expressed by the patient. The investigator will advise the patient to carefully and calmly read the Patient Informed Consent and Consent to the Processing of Personal Data forms and to discuss their contents with their family, friends and doctor before making any decision

in this regard. The patient will give his informed consent by completing and signing the printed Patient Informed Consent and Consent to the Processing of Personal Data forms. From this point on the patient will be considered enrolled in the study.

7.3 Follow-up visit

At the follow-up visit, an objective evaluation of the operated knee will be carried out, questions will be asked about the patient's current state of health, as well as a radiographic follow-up evaluation will be carried out assessing the last anterior-posterior and lateral knee radiographs compared with the first postoperative radiograph.
If the patient has signed the Informed Consent and the Consent to the Processing of Personal Data, the information requested in the case report forms described below will be recorded.

7.4 End of the study

To complete the individual patient study, the recording of all information required in all case report forms must be complete. These forms must also be completed in the event of spontaneous withdrawal from the study, loss of follow-up, failure and surgical revision of the implant. If some information is not available, the blank fields must be crossed out. The study is considered completed once all case report forms have been completed for all patients deemed eligible for the study.

8. Data recording and management

8.1 Case Report Forms (CRF)

For data recording according to this protocol, specific data collection forms, or case report forms (CRF), are prepared. The information reported in anonymous fashion on the CRFs must be recorded for each patient included in the study. Patients will be identified through their name/surname initials following a progressive number. Only the principal investigator will know the 1:1 association between patient and his ID. The CRFs, annexed to this protocol, are the following:

1. *Medical history*. General data of the patient, age, weight, height, diagnosis, medical history, previous medical history, known allergies, osteoporosis.
2. *Intervention*. Prosthetic implant information, the operation date, tibial insert material, whether conventional polyethylene without vitamin E or vitamin E polyethylene (respectively, control group or treatment group), are recorded.
3. *AKSS*. Knee-specific clinical evaluation score that the investigator completes at the last follow-up during the patient's follow-up visit [19].
4. *FJS-12.* Clinical evaluation score on the patient's awareness on his prosthesis, to be filled by the patient himself at the last follow-up [20].
5. *Radiographic evaluation*. Form that the investigators complete by evaluating and comparing the first postoperative radiograph taken after surgery and the anterior-posterior and lateral knee radiographs taken at the last follow-up. The radiographic signs showing the presence of any periprosthetic radiolucency lines or areas of periprosthetic osteolysis, signs of prosthetic loosening and component position will be recorded for each periprosthetic zone according to the “Modern Knee Society Radiographic Evaluation System and Methodology for Total Knee Arthroplasty”.

6. *Complications*. Form to be completed in case of presence of one or more intraoperative or postoperative complications recorded through assessment of the patient's medical records, or at the first telephone contact or during the follow-up visit.
7. *Implant outcome*. Form to be completed to establish whether the patient has been contacted and/or visited, lost to follow-up, or deceased. Furthermore, the outcome of the prosthetic implant, i.e. whether it is still in place and well functioning, whether and when it was failed and surgically removed (revised) or whether it was failed with reoperation but not surgical removed, is recorded. By completing this form, it will be possible to complete the study flowchart like the following shown in Figure 3 to describe the outcome of the entire study population.

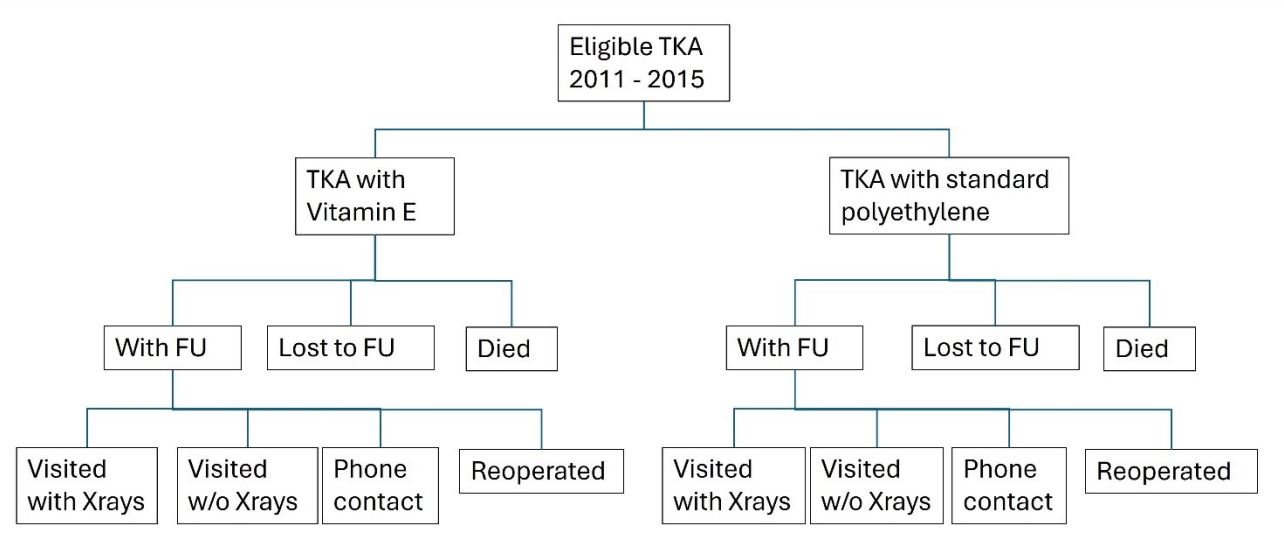

Figure 3. Descriptive flowchart of the study population.

8.2 CRFs completion

The information requested on CRFs are to be recorded by writing with pen on paper printed CRFs.

- The principal investigator is responsible for the completeness and accuracy of the information transcribed on the printed CRF forms.
- No field will be left incomplete without a reason.

8.3 Data entry, analysis and storage

All printed CRFs number 1-7, fully completed and signed in original, must be grouped together in one folder per patient. The original completed CRFs will be stored by the principal investigator in a specific study file, for a period of 15 years at the study centre. A copy of the completed CRFs will be stored by the sponsor in a specific study file, for a period of 15 years at the sponsor facility. Principal investigator and sponsor have the responsibility for data management. The CRF data will be entered by the sponsor into a single electronic database protected by password, which will undergo periodic back-up after each new data entry. The sponsor will have the responsibility for data analysis. At the end of the study, a PDF/A copy of the database file will be stored at the sponsor server and, moreover, will be saved on CD and other external memory and stored at the sponsor facility.

9. Duration of the study

The study will begin following the Ethics Committee approval and after the authorization from the C.O.Q. Management to start the study. A duration of approximately 12 months is estimated for patient screening, telephone contact, follow-up visits and data recording. The study will end with the completion of all the forms required for all enrolled patients. The duration of data entry from the paper CRF format to the electronic database is approximately 1 week but can be carried out at the same time as data collection. An additional 2 months are estimated for data analysis and drafting of the study report.

10. Statistical analysis

10.1 Sample size

In order to calculate the sample size of the study group and the control group, a non-inferiority study is chosen as the most suitable type. Since in the medium term (5-7 years of follow-up), there is reasonably no expectation of significantly better survival results when using a vitamin E polyethylene articular insert compared to a standard polyethylene insert, but rather comparable results. Therefore, we choose to calculate the sample size of the groups using a statistical test of non-inferiority for binary variables (failed implant vs survived implant) of 2 paired groups.

From the prosthetic joint replacement registries of Australia and UK, reports of 2019 and 2018 respectively, the cumulative percentage of revision in total knee arthroplasty with mobile insert is reported as 2.77% at 5 years of follow-up [NJR Report 2018] and 2.8% for HXPE polyethylene inserts at 5 years of follow-up [AUS Report 2019]. The Australian registry also reports 2.3% as the cumulative revision rate for total knee arthroplasty with an insert supplemented with vitamin E at 5 years of follow-up. A difference of at least 4% is considered clinically relevant between survival rates of different knee implants.

Using these failure/survival rates for the control group and the treatment (vitamin E) group, choosing a significance level (alpha) of 5%, a power of 80%, a survival rate of 97.2% for the control and 97.7% for the vitamin E group and with 4% as margin of non-inferiority between both groups, the calculation provides 152 implants per group.

https://www.sealedenvelope.com/power/binary-noninferior/

10.2 Outcome analysis

Cumulative survival is calculated according to the Kaplan-Meier method [21], indicating the 95% confidence interval. Descriptive analysis to summarize the data and study results will be carried out by calculating mean, standard deviation and range of minimum and maximum values for continuous variables and by number and percentage for dichotomous variables. Data distribution was tested for normality with Shapiro-Wilk and D'Agostino Pearson tests.

The analysis of survival rates with 95% confidence intervals of study group versus control group will be performed with logarithmic rank test placing statistical significance at a p-value < 0.05.

The analysis of the differences between the 2 groups regarding the continuous variables will be carried out with Student's t test, while Mann-Whitney U test was used when distribution resulted not normal. The analysis of differences in dichotomous variables will be carried out with Chi-Square or Fisher's Exact tests if at least one of the variables has a value≤5.

The analysis will be carried out with one of the most used statistical software for this type of analysis (GraphPad Prism 10.1.0 Software, Boston, MA, USA).

11. Ethical and regulatory considerations

This clinical investigation is conducted in compliance with the ethical principles set out in the Declaration of Helsinki [22].

11.1 Regulations

The clinical investigation described in this protocol is conducted in compliance with international standards [23], international guidelines, EU MDR 2017/745 [24] and Italian laws currently in force, listed below. The use of personal information collected during this study will take place in accordance with Legislative Decree No. 196, 30 June 2003 and with the European Data Protection Regulation GDPR 2016/679 [25].

11.2 Ethical considerations on the patient

The study aims to verify the survival, results, safety and reliability of a particular prosthetic device used in total knee arthroplasty. This is a cross-sectional study with a retrospective cohort and it will not involve any additional treatment for the patient. The patient has already undergone primary total knee arthroplasty with the investigational device according to the standard procedures provided by the C.O.Q. Orthopaedics Unit. The patient will only be contacted in order to receive his consent to participate in the study, for the compilation of a subjective evaluation form and for the collection of his clinical and radiographic data from visits and radiographic follow-ups normally carried out during normal clinical practice.

11.3 Ethics Committee

This protocol will be presented to the relevant Ethics Committee (EC) for the necessary approval to start the study. The Principal Investigator will communicate to the EC:

a) Request for any deviations from the Study Protocol and reports of deviations from the Protocol, only if the deviation adversely affects the rights, health and well-being of the patient or the scientific integrity of the study;
b) Amendments to any document already approved by the EC;
c) If applicable, any suspension or premature termination of the study;
d) If applicable, justified request to resume the study after its suspension;
e) Final report of the study or its summary.

11.4 Insurance coverage

It is not necessary to take out an insurance policy for the type of study. No additional interventional or diagnostic treatment will be performed on the patient that is not already part of usual clinical practice. The study is observational.

11.5 Confidentiality and protection of patients' personal data

The personal and sensitive data of the patient included in the study will be used exclusively for the purposes of scientific research within the limits and in the manner established by the GDPR EU 2016/679 and by the national regulations that regulate the matter. The personal and sensitive data of the patients enrolled in the study will not be disclosed outside the study centre nor will they be processed by third parties but will be processed only by the Data Processor and by the healthcare personnel appointed by the Data Controller and made available anonymous according to statistical analysis in order to protect the privacy and identity of every single patient involved in the study.

12. Publication Policy

The study promoter/sponsor undertakes to make the results of the trial public in a timely manner, whatever they may be, in accordance with GDPR and privacy legislation. It is in the interest of all the investigators to achieve a peer-reviewed scientific publication of the present study in a journal indexed on PubMed/MEDLINE. Therefore, all the investigators will collaborate in order to draft a scientific original article to be submitted to a selected journal. All information and results related to the present study will be object of possible presentations at congresses before any publication.
Ownership of the data generated from the study will be upon the promoter/sponsor.

13. Costs

The additional costs deriving from the conduct of the Study, such as identification and screening of patients, telephone contact of patients, follow-up visits and recording of study data will be covered by financial coverage provided by the study sponsor, Permedica S.p.A., as according to the study economic agreement. The EC submission fee for study protocol approval is supported by the Sponsor.

14. Amendments to the protocol

All amendments to the protocol following its approval by the EC must be agreed with the principal investigator together with his co-investigators and afterwards will be notified to the EC for their approval by means of a written letter that justify such amendments. Any suspension or early termination of the study will be communicated to the EC.

15. ANNEX

CRFs 1-7

16. References

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17. PROTOCOL APPROVAL

The Investigators, through their signature and date on this page:

- approve this study protocol;
- declare that the study will be conducted in accordance with what is reported in this protocol.

Name and surname of the investigator (*principal)	Position	Signature	Date
Marco Spezia*	Head of the Management of the Surgical Unit and Director of the C.O.Q. Orthopedic Unit of Omegna		
Alessandro Masse'	Director of Complex Unit 1 Orthopaedics and Traumatology CTO of Turin.		
Lorenzo Banci	Head of Clinical Research Permedica SpA of Merate.		

17. APPROVAZIONE DEL PROTOCOLLO

Gli Sperimentatori, mediante la loro firma e data su questa pagina:

- approvano il presente Protocollo;
- dichiarano che lo Studio verrà condotto in conformità a quanto riportato nel presente protocollo.

Nome e cognome dello sperimentatore (*principale)	Posizione	Firma	Data
Marco Spezia*	Responsabile della Direzione dell'Unità Chirurgica e Direttore Unità Ortopedica COQ di Omegna	REGIONE PIEMONTE - A.S.L. V.C.O. - VB CENTRO ORTOPEDICO DI QUADRANTE 010896 Dr. Spezia Marco Specialista in Ortopedia e Traumatologia C.F. SPZ MRC 62M14 H037P Iscrizione albo N. [illegible] (V.C.O.)	20/10/2020
Alessandro Masse'	Direttore Struttura Complessa Unità 1 Ortopedia e Traumatologia CTO di Torino.	A.O.U. Città della Salute e della Scienza di Torino S.C. ORTOPEDIA E TRAUMATOLOGIA 1U Direttore: Prof. Alessandro MASSE'	21/10/2020
Lorenzo Banci	Responsabile Ricerca Clinica Permedica S.p.A di Merate.		20/10/2020
ALESSANDRO BISTOLFI	Clinica Ortopedica	AOU Città della Salute e della Scienza di Torino P.O. CTO S.C. ORTOP. E TRAUMAT. 1 U Dott. Alessandro BISTOLFI	19/10/2020