ORIGIN® vs. VANGUARD® PS

Protocol title	**A post-market observational ORIGIN® vs. VANGUARD® PS clinical study: a comparative, prospective, randomized controlled clinical and radiological evaluation.**
Protocol ID	CLIN-G-010
Protocol title	ORIGIN® vs. VANGUARD® PS
Protocol Date / version	08 DEC 2020. / version 1.4
Sponsor	Symbios Orthopedie SA Avenue des Sciences 1, 1400 Yverdon-les-Bains, Switzerland
Institution **(Investigational Site)**	University Medical Center of Johannes Gutenberg-University Mainz (UMC- Mainz) Address: Langenbeckstrasse 1 55131 Mainz Germany
External Partners	Trium (CRO) & Bepatient (eCRF)
Reference ID (EC) if applicable:	2019-14580 (Landersarztekammer Rheinland-Pfalz)

REVIEW AND APPROVAL:

	Name	*Title*	*Date*	*Signature*
Author	Bojana GANNEVAT	**Clinical Affairs Manager**		
	Sven HOFER	**Expert Statistics**		
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PARTICIPATING INVESTIGATORS (INV):

Institutions	*Name of INV*	*Title*	*Date*	*Signature*
University Mainz	Prof. Dr. Drees	Principal Investigator		
University Mainz	Dr. Klonschinski	Co-Investigator		
University Mainz	Dr. Eckhard	Co-Investigator		

CONFIDENTAL AND PROPRIETARY:

CHANGE HISTORY RECORD:

CIP Change History		
Version	**Summary of Changes**	**Author**
1.1	Initial Release	Julie Ledieu
1.2	Review N°1	Julie Ledieu
1.3	Revision N°2	Bojana Gannevat
1.4	Revision N°3	Bojana Gannevat

SIGNATURE PAGE

STUDY TITLE: **ORIGIN® vs. VANGUARD® PS**

VERSION CLINICAL INVESTIGATION PLAN: **Version 1.4, 08-DEC-2020**

I have read the above named Clinical Investigational Plan and agree to conduct the trial as outlined and in compliance with country, local and internal institutional requirements.

Name of Institution: _____

Name Principal Investigator: _____

_____ _____

Principal Investigator Signature Date: dd mmm yyyy

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I.CLINICAL INVESTIGATION PLAN - SYNOPSIS

SYMBIOS Device	ORIGIN®
Protocol ID:	CLIN-G-010
Protocol Date / Version:	08.DEC.2020 / version 1.4
Protocol title:	ORIGIN® vs. VANGUARD® PS
Study Purpose:	The study primary objective is: To assess patient satisfaction after the surgery with a custom-made CE marked implant (ORIGIN®) versus off-the-shelf (VANGUARD PS) device. Document the clinical and device performance outcomes of ORIGIN SYSTEM used in routine hospital practice in a large patient cohort in treatment of Total Knee Replacement. No additional radiological, clinical, or biological exams, compared to routine practice
Study design:	Prospective, comparative, randomized (1:1), double-arm, mono-centric (Germany), observational, post market study
Study sponsor:	Symbios Orthopédie SA Avenue des Sciences 1 1400 YVERDON LES BAINS, Suisse www.symbios.ch
Investigators:	Designated Orthopedic surgeons (Prof. Drees as Principal Investigator and Drs. Eckhard and Klonschinski (as co-Investigators) from University in Mainz) who are willing to participate in this study and who have previously informed patients on the design of the study and collection of data
Investigational device: Arm 1	ORIGINPS CE Marked device
Comparative device: Arm 2	VANGUARD® PS CE Marked
Therapeutic Indication:	The knee prostheses are intended to be used in first intention cemented Total Knee Arthroplasty. • Severe painful and/or disabled knee joint, resulting from: - Non-inflammatory degenerative knee joint disease - Osteoarthritis, necrosis, post traumatic arthritis • Inflammatory knee joint disease:

SYMBIOS Device	ORIGIN®
	- Rheumatoid arthritis
Study endpoints:	• **Primary endpoint:** o To compare the ability of patients to forget their operated knee at 1 year after the surgery, measured by the Forgotten Joint Score 12 (FJS-12 Knee). The goal is to assess patient satisfaction regarding the surgery with a CE marked custom-made implant (ORIGIN®) versus off-the-shelf (VANGUARD PS) device with a self-administrated patient satisfaction questionnaire. • **Secondary endpoints:** o Evaluate the success of the procedure o Evaluate outcomes & complications & revision rate with the ORIGIN SYSTEM versus VANGUARD PS at the last (2y) follow-up visit o Evaluate performance of the ORIGIN System vs VANGUARD PS at 2 years follow-up: clinical examination and scoring. To evaluate/compare the clinical, functional and quality of life outcomes using the following **scores:** o The Knee Injury and Osteoarthritis Outcome Score (KOOS) o The Oxford Knee Score (OKS) o The EQ-5D-5L Score o A self-administrated patient satisfaction questionnaire. o Evaluate the radiographic limb alignment, radiolucent lines and radiographic loosening (according to the "Modern Knee Society Radiographic Evaluation System and Methodology for Total Knee Arthroplasty" version 2015) o To evaluate/compare the radiological results (measurements and observations by surgeon reported scores: o The Knee Society Score (KSS) (Objective Knee Indicators only) o Knee Society Radiographic Evaluation and Scoring System (KSRESS) o The Single Leg Stance Test (SLS) o The Timed Up & Go test (TUG)
N sites	1 – UMC MAINZ
Sample size	140
	However, enrollment will occur at the time of the medical examination. It is assumed that the subjects' treatments and follow-up visits will be performed per standard of care in the participating site
Total study duration:	48 months
	- Start- up phase: 3 months - Enrolment: 18 months - Follow-up phase: 24 months - Study closure: 3 months

SYMBIOS Device	ORIGIN®
N of FU visits:	4
Follow-up visits:	Preop / Surgery / 1y / 2y Follow-up visits
Study start date:	DEC 2020
Date first visit first patient:	JAN 2021
Study Scoring:	Forgotten Joint score (FJS) KOOS Score OKS Score EQ-5D-5L Score A self-administrated patient satisfaction questionnaire (3 questions)
Inclusion criteria:	Symbios plans to include consecutive eligible subjects which will be treated either with the ORIGIN SYSTEM versus VANGUARD PS. Subjects will be enrolled upon evaluation via a clinical examination at the preoperative stage. Subjects should meet the following criteria: • Male and female over 18 years of age • Each patient, or his or her guardian or legal representative, is willing to give informed consent. • Clinically indicated for a total Knee replacement • Females who are not pregnant or lactating and not planning to become pregnant ≤ 12 months. A pregnancy test may be performed to confirm this. • Geographically stable and willing to return to the implanting site for all follow-up visits at 1 year and 2 years.
Exclusion criteria:	Patients meeting any one of the following criteria will be excluded from participating in this study: • Life expectancy ≤ 1 year • Age ≥ 80 years • Acute or chronic, local or systemic infection • Mental illness • Muscular, ligamental, neurological, psychological or vascular deficits • Bone destruction or poor bone quality likely to affect implant stability (requiring a femoral and/or a tibial stem and/or a thick insert) • Any concomitant condition likely to affect implant integration or function • Allergy or hypersensitivity to any of the materials used • For devices in CoCrMo (ISO 5832/4): renal and hepatic impairment • Hip Knee Ankle (HKA) angle < 165° or > 195°

SYMBIOS Device	ORIGIN®
	• Severe collateral ligaments deficiency (requiring a more constrained prosthesis) • Major anatomical deformities • Severe flexion contracture or severe recurvatum • Revision of a partial or total knee prosthesis • Non-extractible material (e.g. screws, plate, intramedullary nail, osteosynthesis material…) which can create a conflict with any component of the prosthesis • Distal and/or posterior and/or anterior femoral bone loss which exceeds the femoral component thickness • Proximal tibial bone loss which exceeds the tibial component thickness (tibial tray + tibial insert) • Allergy of any implant material
Collected data:	• **Baseline data:** Year of birth, gender, weight, height, BMI, indication, medical knee history (number of surgeries, description, patient outcome), radiological examination or CT scan • **Surgery procedure:** side of implantation, implanted devices ORIGIN (instruments included) vs VANGUARD PS, surgery total duration time, perioperative complications and difficulties, Surgeon satisfaction regarding devices and instruments, Femoral and tibial sizing, patellar resurfacing. • **Postoperative Follow-up:** (1y, 2y) follow-up visits: Physical examination, weight, height, BMI Rx examination, safety evaluation, scoring via a questionnaire: FJS score (at 1y and 2y FU visits), patient satisfaction, surgeon reported scores (Knee Society Radiographic Evaluation and Scoring System (KSRESS, the Knee Society Score (KSS) (Objective Knee Indicators only), the Single Leg Stance Test (SLS) , the Timed Up & Go test (TUG))and patient reported scores: KOOS, OKS, FJS; EQ-5D-5L, a self-administrated patient satisfaction questionnaire and complications, revisions. FJS and other reported scores (at the postoperative visits) will be collected per standard of care at the investigational site and will be compared at each follow-up among ARM 1 and 2.
Clinical Affairs Manager:	Bojana Gannevat
Clinical Monitor:	TRIUM (Clinical Monitor)
eCRF platform:	Bepatient

II. INTRODUCTION

ORIGIN® PS and VANGUARD® PS are total knee prostheses, intended to be used in primary Total Knee Replacement Arthroplasty (TKA) (cf. detailed products description page 12). With the ORIGIN® PS implant being customized individually made (CIM) fitting a patient's anatomy, a more natural reconstruction of knee kinematics is anticipated and ultimately a higher patient satisfaction and lower revision rate are envisioned. To date literature providing data about CIM TKA is still scarce. A study by Patil et al. assessing kinematics after TKA found that CIM TKA more closely resembled natural knee kinematics when compared to standard off-the-shelf (OTS) TKA (Patil S et al. Knee. 2015). This resemblance allows for a more natural femoral rollback during knee flexion, the authors found. Zeller et al. also came to the conclusion, that CIM TKA demonstrates knee kinematics more similar to a normal knee studying tibiofemoral kinematics using mobile fluoroscopy in vivo (Zeller IM et al. J Arthroplasty. 2017). Furthermore, CIM TKA has shown to provide a more accurate tibial fit and rotation, when compared to several standard TKA (Schroeder L et al. J Knee Surg. 2019).

A retrospective review of 621 TKA patients, 307 with CIM TKA and 314 with conventional implants, demonstrated a decreased estimated blood loss, decreased length of stay, decreased range of motion, and no discernible difference in surgical or tourniquet time (Schwarzkopf R et al. Orthop J Sports Med. 2015). Albeit, the differences found were not deemed clinically relevant, the study underlined the safety and efficacy of the CIM TKA technique. Hospital outcomes of 248 consecutive TKA patients (126 CIM TKA, 122 OTS TKA) were analyzed by Culler et al. (Culler SD et al. Arthroplast Today. 2017). Patients who received CIM TKA had lower transfusion rates and fewer adverse events.

Four year data from the UK National Joint Registry showed a cumulative percent revision rate of 0.5% for CIM TKA versus a cumulative percent revision rate of 1.9% for all TKA (National Joint Registry for England, Wales, Northern Ireland and the Isle of Man; 15th Annual Report 2018).

While all this data is encouraging, randomized controlled studies and assessments of patient reported outcomes are missing. Therefore, the current study aims to close this knowledge gap and provide Level I evidence for CIM TKA by comparing the two TKA Prostheses mentioned above and to evaluate their clinical performance and safety.

III. DESCRIPTION OF THE DEVICE UNDER EVALUATION

A. Summary description of ORIGIN®

a) *General characteristics*

ORIGIN® PS Total Knee Prosthesis is designed to deliver an orthopedic solution to a patient in need of a total knee arthroplasty, by finding among a large range of femoral and tibial component shapes, the prosthetic device matching the most the patient's knee anatomy (patient specific prosthesis).

The ORIGIN® Knee System is a set of implants and single use instruments (personalized or not) for each patient.

	Implants	Instruments
Manufacturer	Symbios Orthopedie SA	
Name	ORIGIN®	ORIGIN® KNEE-PLAN® Guides ORIGIN® KNEE-PLAN® Set
Components	Femoral component: *ORIGIN® PS Femur Cemented* (5000 1100)	ORIGIN® KNEE-PLAN® Guides
	Tibial inserts: *ORIGIN® PS Fixed Inserts* (5000 3100 or 5000 3102)	ORIGIN® Femur set
	Tibial tray: *ORIGIN® Fixed Tibia Monobloc Cemented* (5000 2100) or ORIGIN PS Fixed Tibia Modular Cemented (5000 2300) or ORIGIN Modular Stem (5000 370X)	ORIGIN® Tibia set or ORIGIN PS Tibia Modular Set
	Patellar component: *ORIGIN® Patella Cemented* (5000 410X)	Knee Impaction Set
		Add-on box
CE marking	☒ CE-marked	
European Directive	☒ Medical Devices (MDD) ☐ Active Implantable MD (AIMDD) ☐ MDR 2017/745	
Class	☒ Class III	☒ Class I ☒ Class IIa

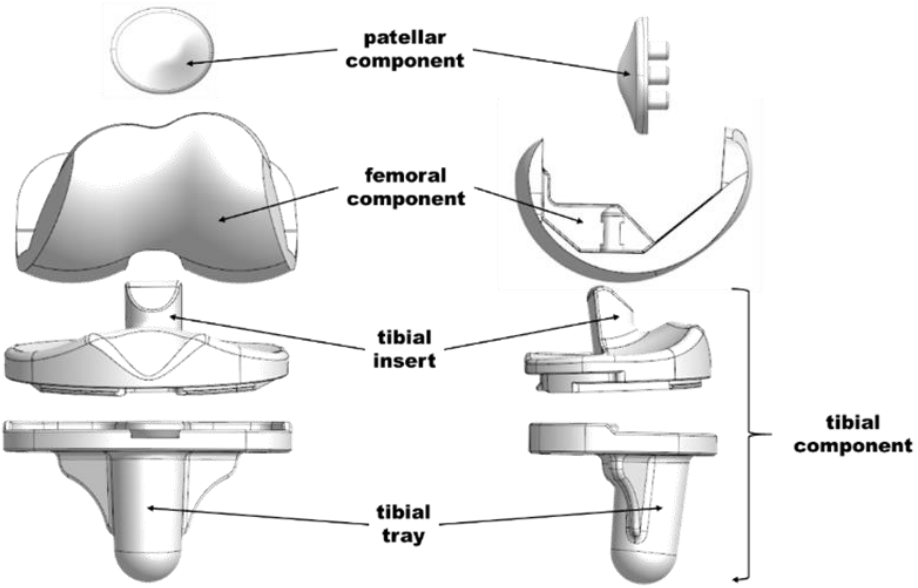
b) *Implants*

ORIGIN® is made of 4 components:

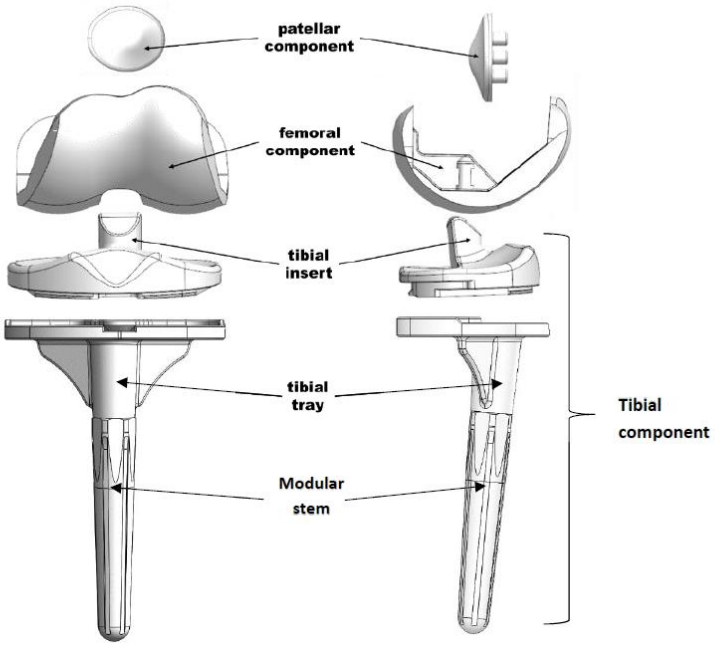
Name	Component type	Component type description according to ISO 7207-1:2007
ORIGIN® PS Femur cemented	Femoral component	§ 3.2.3: "Femoral component: component of total, patella-femoral or unicompartmental knee joint prosthesis intended to be secured to the femur to replace its articulating surface(s)"
ORIGIN® PS Fixed Insert	Tibial Insert (o-2mm)	§ 3.2.9: "tibial insert: sub-component of a modular tibial component of a total or unicompartmental knee joint prosthesis which is attached to the tibial tray and which articulates with the femoral component"
ORIGIN® PS Fixed Tibia	Tibial Tray Monobloc & Modular cemented[1]	§ 3.2.8: "sub-component of a modular tibial component of a total or unicompartmental knee joint prosthesis used to support the tibial insert or mobile bearing component"
ORIGIN® Patella	Patellar component	§ 3.2.13: "component of total or patello-femoral knee joint prosthesis which is used to replace the articulating surface of the patella"

ORIGIN PS Fixed Tibia MONOBLOC Cemented:

[1] A modular tibia stem can be added per surgeon request in case of high BMI, poor bone quality, Very active patient, large limb axis deviation, Oblique bony cuts



ORIGIN PS Fixed Tibia MODULAR Cemented:

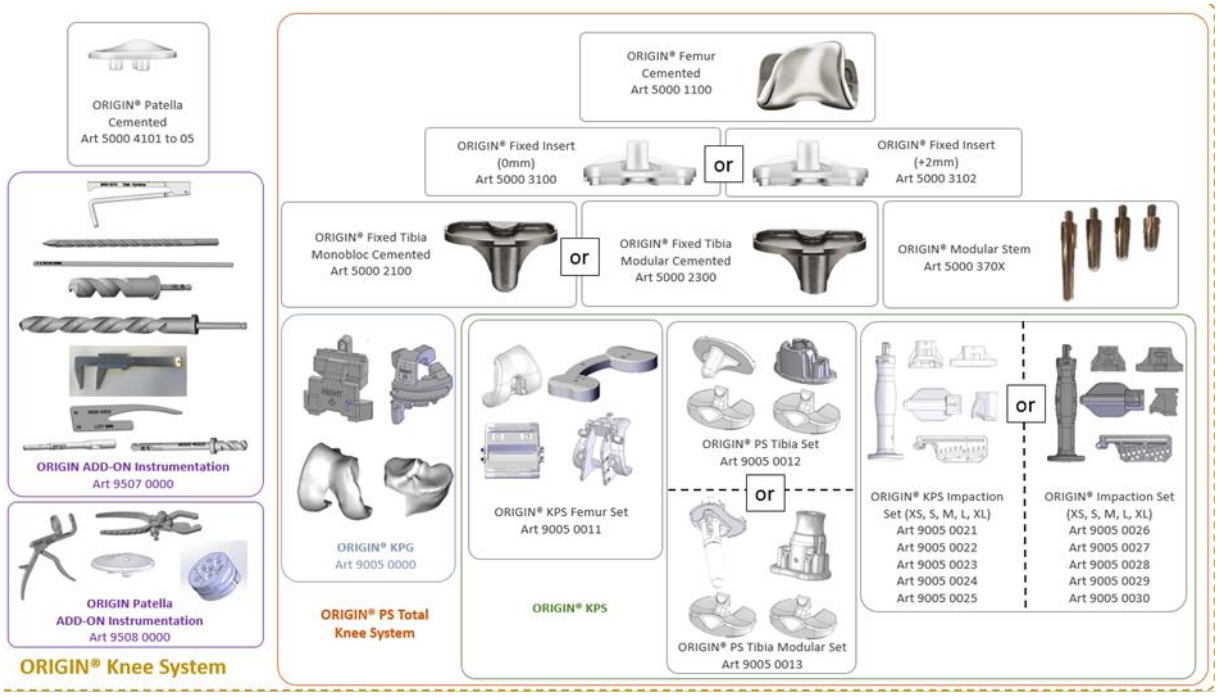


c) *Instruments*

- ORIGIN® Knee-Plan Guides (KPG) are single-use personalized instruments that allow to perform femoral and tibial bone cuts.

- ORIGIN® Knee-Plan Set (KPS) is the single use instrumentation that allows the other bone cuts, recuts and the reduction trials. Parts of the instrumentation is personalized, some parts are standard, but the correct size is chosen for the specific patient and other instruments are standard.

- The ADD-ON box contains re-usable instruments such as drills and pins for fixation of the Knee-Plan Guides and Knee-Plan Set instruments. This box also contains instruments for patellar replacement and trials.



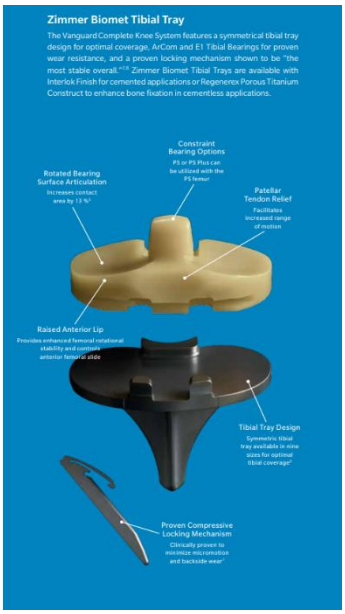
d) *ORIGIN planning flowchart*

B. Summary description of VANGUARD® PS

The Vanguard Knee System offers surgical simplicity to knee arthroplasty with its bearing versatility and complete component interchangeability. The independent fit of the femoral, tibial, and patellar components allows surgeons to provide tailored patient care. The Vanguard Knee System offers an entire spectrum of knee stability, including:

- Two femoral stabilization options: cruciate retaining (CR) and posterior stabilized (PS)
- Ten femoral sizes
- Nine tibial sizes
- Five levels of bearing constraint
- Complete interchangeability between femoral and tibial components
- Optimal congruency in the coronal plane resulting from Zimmer Biomet's proprietary 1:1 conformity
- Twenty-six patella options in multiple diameters, thicknesses, and peg configurations
- Three fully interchangeable instrument platforms
- Part of the surgical simplicity is the overall performance surgeons and their patients can rely on with Zimmer Biomet orthopedic implants (cf. Biomet brochure) [2]

[2] https://www.zimmerbiomet.com/medical-professionals/knee/product/vanguard-knee.html

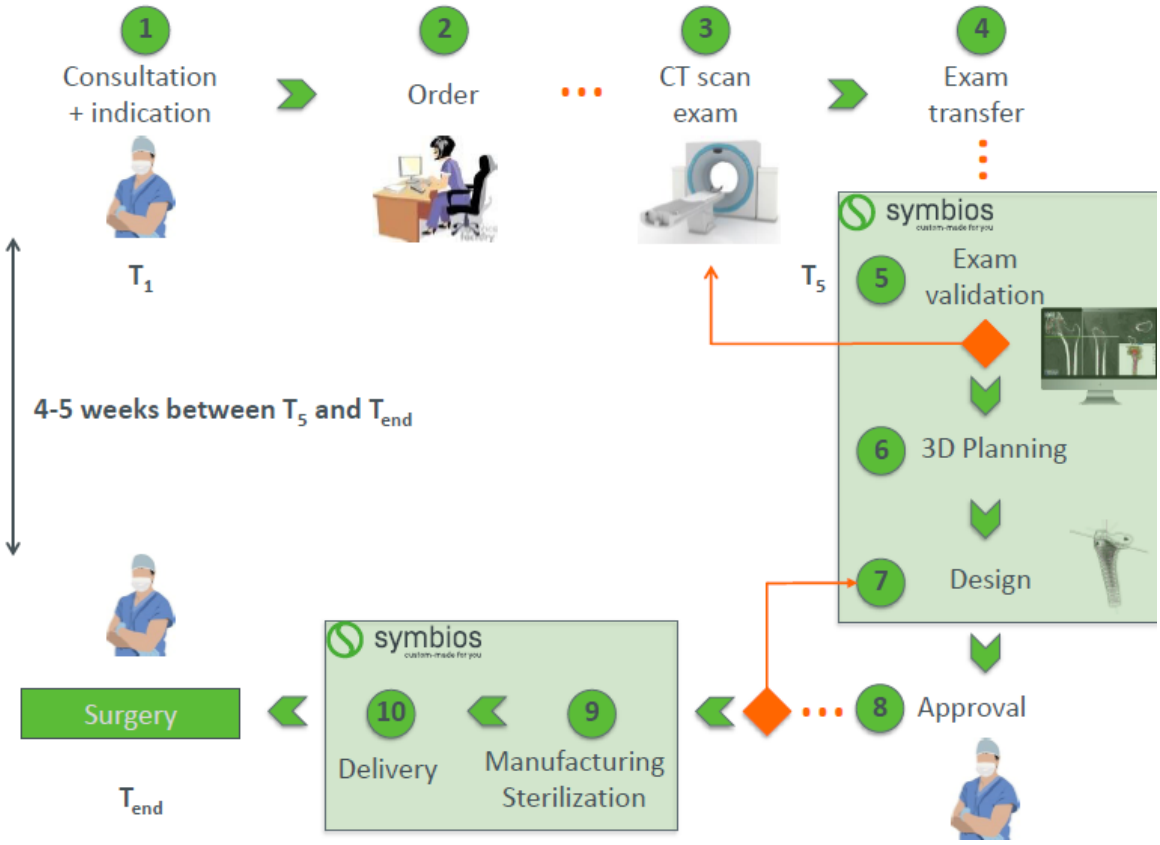


C. Intended purpose

The Biomet Vanguard Complete Knee System prosthesis (Biomet Inc, Warsaw, IN) is intended to be used for performing primary Total Knee Replacement. It has been on the market in the United States and in Europe for over 10 years and has demonstrated excellent survivorship.

The ORIGIN® Knee System is intended to be used for performing primary Total Knee Replacement in patient suffering from non-inflammatory degenerative and inflammatory knee joint disease.

The ORIGIN® Knee System has been launched on the market since September 2018. To date, 1509 prostheses have been implanted. The following process describes how ORIGIN implants and instruments are drawn, planned and manufactured.



D. Study population

Patients who have provided consent for participating in this study and met the protocol eligibility criteria will be enrolled into this observational comparative randomized (1:1) prospective monocentric study.

E. Indications and contraindications for ORIGIN® PS

INDICATIONS:

- Severe painful and/or disabled knee joint, resulting from:
  - Non-inflammatory degenerative knee joint disease
  - Osteoarthritis, necrosis, post traumatic arthritis
- Or Inflammatory knee joint disease
  - Rheumatoid arthritis

CONTRAINDICATIONS:

- Acute or chronic, local or systemic infection

- Muscular, ligamental, neurological, psychological or vascular deficits
- Bone destruction or poor bone quality likely to affect implant stability (requiring a femoral and/or a tibial stem and/or a thick insert)
- Any concomitant condition likely to affect implant integration or function
- Allergy or hypersensitivity to any of the materials used
- For devices in CoCrMo (ISO 5832/4): renal and hepatic impairment
- Hip Knee Ankle (HKA) angle < 165° or > 195°
- Severe collateral ligaments deficiency (requiring a more constrained prosthesis)
- Major anatomical deformities
- Severe flexion contracture or severe recurvatum
- Revision of a partial or total knee prosthesis
- Non-extractible material (e.g. screws, plate, intramedullary nail, osteosynthesis material…) which can create a conflict with any component of the prosthesis
- Distal and/or posterior and/or anterior femoral bone loss which exceeds the femoral component thickness
- Proximal tibial bone loss which exceeds the tibial component thickness (tibial tray + tibial insert)
- Need of a stem

F. Description of medical procedure

The medical procedure is performed according to the standard procedures of the surgeon at the hospital. The surgical approach should be performed according the Instruction for Use of the ORIGIN System. Regarding VANGUARD® PS, the operative technique is in accordance with the surgical technique guide provided by Biomet. Surgery will be performed or supervised by an experienced orthopedic surgeon.

In this protocol, ORIGIN® PS will be described based on main following surgical steps:

- STEP 1: Incision and exposure
  - Surgical approach
  - Exposure for applying the guides
  - Anterior and posterior cruciate ligaments resection

- STEP 2: Distal femoral cut
  - Examination of femoral bone model and femoral cutting guide
  - Initial positioning of the femoral cutting guide
  - Marking out the support zones on the patient's bone
  - Resection of remaining cartilage on the support zones
  - Controlling femoral cutting guide stability and fixation
  - Controlling the frontal alignment
  - Controlling the resection level
  - Stabilizing the femoral cutting guide for the distal cut

- Mark the holes for the 4-in-1 cutting block
- Distal femoral cut

- STEP 3: Proximal tibial cut
  - Examination of tibial bone model and tibial cutting guide
  - Cleaning of soft tissue on the tibial support zones
  - Initial positioning of the tibial cutting guide
  - Marking out the support zones on the patient's bone
  - Resection of remaining cartilage on the support zones
  - Controlling tibial cutting guide stability and fixation
  - Controlling the frontal alignment
  - Controlling the resection level
  - Stabilizing the tibial cutting guide for the proximal cut
  - Proximal tibial cut
  - Comparing the resection with the bone model

- STEP 4: Extension controls
  - Controlling the extension gap and ligament balancing
  - Controlling the frontal alignment in extension

- STEP 5: Antero-posterior femoral cuts and chamfer cuts
  - Positioning of distal drill pins
  - Positioning of the 4-in-1 cutting block
  - Controlling anterior and posterior resections
  - Stabilization of the block for antero-posterior cuts
  - Antero-posterior femoral cuts and chamfer cuts
  - Finishing steps

- STEP 6: Flexion controls
  - Controlling the flexion gap and ligament balancing

- STEP 7: Intercondylar cuts
  - Positioning and fixation of the block
  - Preparing the holes for the femoral component legs
  - Cuts in the intercondylar notch
  - Trochlear central reinforcement cut
  - Bone cleaning and preparation of the intercondylar notch

- STEP 8: Intercondylar cuts
  - Placement of the tibial trial base plate with the planned rotation
  - Fixation of the tibial trial base plate
  - Drilling the lateral anchoring peg holes
  - Preparatory drilling for the tibial keel

- STEP 9: Trials

- Placement of the trial tibial stem
- Placement of the trial tibial insert
- Placement of the trial femoral component
- Controlling knee stability and mobility

- STEP 10: Tibial imprint compaction
  - Compaction of tibial imprint

- STEP 11: Patellar preparation (optional)
  - Exposing the patella
  - Placement of the patella cutting clamp
  - Adjusting resection height
  - Patellar cut
  - Determining the patella size
  - Placement of the clamp and drilling

- STEP 12: Implantation
  - Tibial base plate
  - Tibial insert
  - Femoral component
  - Patellar component
  - Trials on definitive implants and closure

Cf. List of Instruments in Chapter XXI APPENDICES

G. Summary of necessary training and experience

The PI will ensure that the investigational site has the appropriate support staff to execute the trial. Additional staff may include co-investigators, research coordinators, and other specialized health care professionals. The PI will document authorization of delegated tasks using the Delegation of Tasks Log provided by Symbios. Staff is trained and experienced to perform surgeries as described in the surgical technics for both ORIGIN & VANGUARD Systems.

Prior to investigational site activation or subsequent involvement in clinical study activities, Symbios or designated CRO will provide clinical study training relevant and pertinent to the involvement of personnel conducting clinical study activities, including investigator responsibilities, ISO 14155, the CIP, PIC, use of data collection tools and applicable local regulations.
All study personnel should be trained in accordance to their responsibilities (as documented on the Delegated Task List) and no study-specific activities should be performed before training is complete.

IV.JUSTIFICATION OF THE STUDY DESIGN

A. Evaluation of pre-clinic data (if applicable)

Currently no pre-clinical studies have been performed on the device under evaluation named as ORIGIN. The pre-clinical data regarding the VANGUARD system are the property of Biomet and are not collected for the purpose of this study.

B. Evaluation of relevant clinical data (Registries, PMS, PMCFs)

As part of Symbios PMS, a prospective surveillance is established on the evaluated device. It includes the surveillance of all relevant scientific journals and regular electronic database (EMBASE, PubMed) review. A list of pertinent publications for this study is in the section XX. BIBLIOGRAPHY.
post-market surveillance also includes the current ongoing Symbios PMCF study CLIN-G-008: Evaluation of the performance and the safety of the ORIGIN® knee prosthesis and of the KNEE-PLAN® ORIGIN® instruments. (Study launched in 2018)
This study is related to 399 primary Total Knee Replacements, performed between 2018 and 2020. Indications are coherent with Instructions for Use. The mean follow-up is 1.0 year (max 1.6 year)
Preliminary results:

- Number of procedures 399
- Gender Females 52 % / Males 48 %
- Age Mean 71.0 years
- Mean weight 81.1 kg (33-177)
- Mean height 168.7 cm (143-193)
- Mean Body Mass Index 28.4 (13-68)

Outcomes regarding performance:

- ➢ FJS score: compared to preoperative value, the Forgotten Joint Score is significantly improved at 3-6 months and at 1 year. According to the validated grading, the mean preoperative score (12.9/100) is poor and the mean score at 3-6 months (42/100) and at 1 year (60.5/100) is good

- ➢ Oxford Knee Score: compared to preoperative value, the Oxford Knee Score is significantly improved at 3-6 months and 1 year. According to the validated grading, the mean preoperative score (24.8/48) is poor and the mean score at 3-6 months (36.6/48) and at 1 year (41.2/48) is good

- ✓ Many of the patients are satisfied about their surgery (96% of satisfied or very satisfied)

<u>At a mean follow-up of 1.0 year</u>:

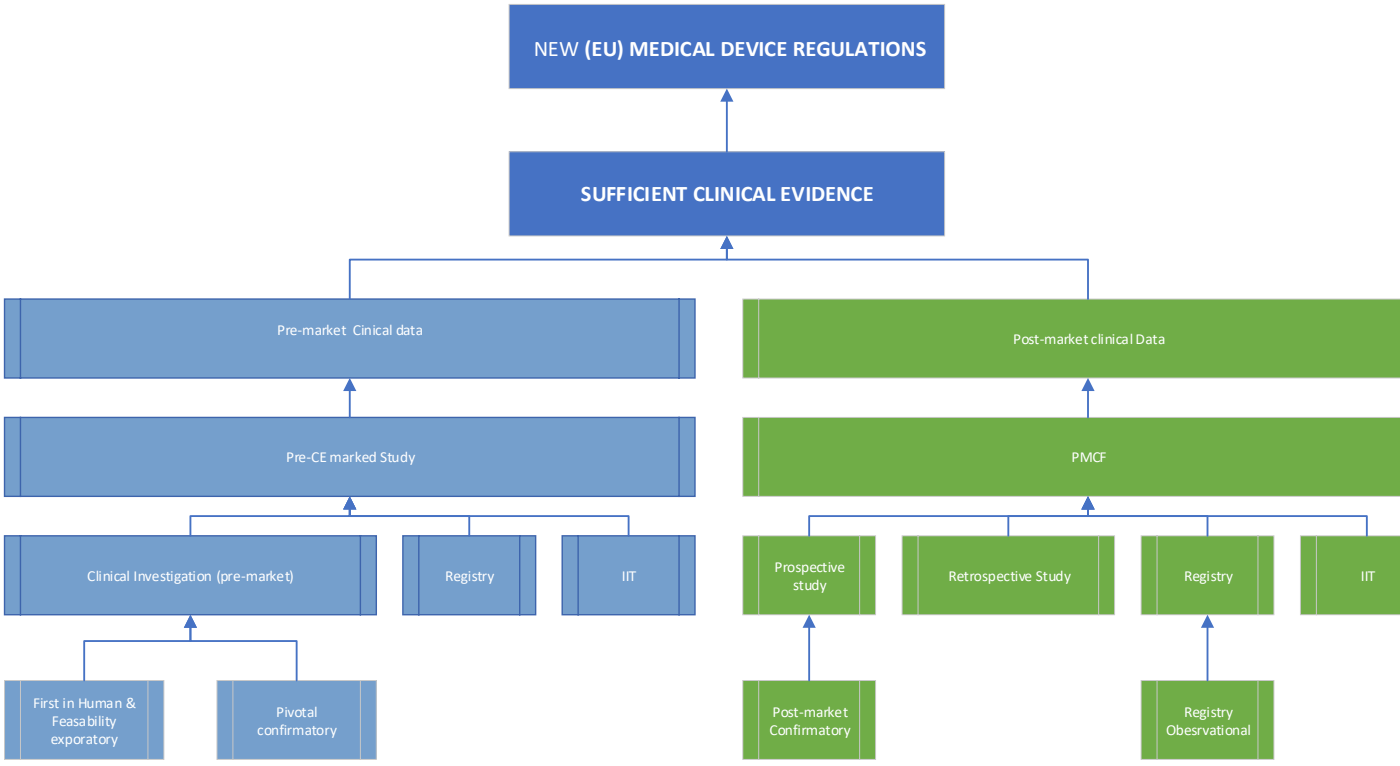
- ✓ The per-operative complication rate is 0.25%

- ✓ The postoperative complication rate without revision is 3.25%
- ✓ The postoperative complication rate with revision is 0.25%

The ORIGIN® Knee system is also followed in the UK National Joint Registry. The last Post-Market Surveillance (PMS) report is related to 19 primary Total Knee Replacement, surgeries were performed from December 2018 to January 2020. Indications are coherent with Instructions for Use. The mean follow-up is 0.6 years (max 1.2 years). At a mean follow-up of 0.6 year, the revision rate is 5.3 %.
Clinical data to date are analyzed at short-term follow-up and need to be monitored at medium and long-term. (up to 10 years)

C. Description of clinical development stage

The clinical development stages are part of global Symbios Clinical Strategy for Symbios products, during overall product lifecycle. ORIGIN is a medical device system followed in PMCF studies and registries (UK & SWITZERLAND) as part of post-market surveillance to compile sufficient data for Clinical Evidence.



D. Post-Market Surveillance

Participation in this clinical study will not result in any direct benefit to the patient. Trial subjects implanted with ORIGIN System receive the same medical treatment as if they were not participating in this post-market study. Participation contributes to expansion of the knowledge base with respect to the use of the ORIGIN system in a routine hospital setting. This observational study will be used as part

of clinical evaluation and post-market surveillance of the evaluated device. Results will be used to support the update of the Clinical Evaluation Report (CER) and Post-Market Surveillance Report (PMS).

V.RISKS AND BENEFICES OF THE EVALUATED DEVICE

A. Anticipated clinical benefits

Participation in this clinical study will not result in any direct benefit to the patient. Trial subjects implanted with ORIGIN/VANGUARD, both CE marked devices, receive the same medical treatment as if they were not participating in this post-market study. This is emphasized by the fact that randomized controlled studies and assessments of patient reported outcomes are missing in the current scientific knowledge. Therefore, the current study aims to narrow this knowledge gap and provide Level of evidence for TKA by comparing the two similar TKA Prostheses mentioned above and to evaluate their clinical performance and safety.

However, the expected benefits of the ORIGIN® implants is to reduce the knee pain, increase the knee mobility, provide a stable knee, increase the knee function, and increase the quality of life of patients.

The hypothesis raised for this study, regarding the scoring, is that patients will experience a marked improvement in the natural feel of the prosthesis during the first year after the surgery, and slightly significant improvement at the following interval of 2 years. The overall patient satisfaction is expected to be improved after 2 years follow-up whether they receive ORIGIN or VANGUARD

B. Residual risks

ORIGIN® Knee Implants has no innovative aspects compared to standard posterior-stabilized Total Knee Prosthesis. All the possible adverse events potentially caused by the implantation of ORIGIN® Knee Implants are known in the state of the art. These are also listed in the Instruction for Use of the evaluated devices, as listed below.

Adverse events	Severity	Probability in CER	Probability	Reduced risk score	Unanticipated Intolerable Harms?	Risk control measures
Infection	8	0.2 %	2		☐ yes ☒ no	NA
Aseptic loosening	6	0.2 %	4		☐ yes ☒ no	NA
Pain	6	0.7 %	4		☐ yes ☒ no	NA
Stiffness	6	2.2 %	6		☐ yes ☒ no	Monitored through PMCF/PMS
Malalignment	4	0 %	2		☐ yes ☒ no	NA
Instability	4	0 %	2		☐ yes ☒ no	NA
Dislocation/Subluxation	6	0 %	2		☐ yes ☒ no	NA
Periprosthetic fracture	8	0.2 %	4		☐ yes ☒ no	Monitored through PMCF/PMS

Wear	4	0 %	2		☐ yes ☒ no	NA
Adverse Soft tissues/lysis	6	0 %	2		☐ yes ☒ no	NA
Allergy	6	0 %	2		☐ yes ☒ no	NA
Component dissociation	8	0 %	2		☐ yes ☒ no	NA
Implant fracture	8	0 %	2		☐ yes ☒ no	NA

Stiffness is a common early adverse event identified in subjects who underwent a surgical procedure with the ORIGIN System.
Infection is also an identified postoperative adverse event as occurring to subjects who underwent a surgical procedure with the ORIGIN System.

The residual risks are monitored through a post-market surveillance, vigilance and customer feedback.

C. Risks associated with participation in the clinical investigation

There are possible risks and side effects connected to the ORIGIN & VANGUARD implants (as described in the IFU), but the risks are similar to those for an implant of the ORIGIN & VANGUARD without participation in this study. The risks are known and consistent with the state of the art.

Clinical data to date for ORIGIN system are analyzed at short-term follow-up and need to be monitored at medium and long-term (up to 10 years).

Risks and events will be continuously monitored, assessed and documented by the investigator. Instructions for Use is a reference for the list of anticipated adverse events which may be associated with the use of the ORIGIN & VANGUARD System.

D. Risks-to-benefit rationale

Appropriate risk management activities have been performed for ORIGIN system resulting in a positive risk-to-benefit rationale as confirmed by CE mark. Risks and potential benefits are similar for subjects being implanted as part of this study protocol compared to subjects implanted while not participating in this study. Symbios risk management report applied to the ORIGIN Knee System, is part of the technical file compilation and maintenance, and post-production activities of the product's lifecycle.

VI. STUDY OBJECTIVES

A. Study purpose

The study objective is to assess patient satisfaction prior and after the surgery and to document the clinical and device performance outcomes of the ORIGIN System used in routine hospital practice in a large patient cohort treatment of total knee arthroplasty.

a) *Performance claim*

All data related to the evaluated device are part of Symbios clinical evaluation. Therefore, the performance claim is validated by the clinical evaluation.

b) *Safety claim*

The safety claim for the ORIGIN System is validated by the clinical evaluation. The revision rate is consistent with the state of the art. With a confidence interval of 95%, the revision rate is not higher than 2% at 1 year.

Specific claims for clinical performance and effectiveness of the ORIGIN System, is based on the state-of-the-art and is described in the clinical evaluation for the evaluated product.

The basis for the selection of the study endpoints includes the following considerations:

- They are clinically relevant and address important safety and efficacy aspects of the ORIGIN System.
- They are objectively defined and measurable in most subjects.
- They are consistent with current recommendations for endpoints in TKA clinical studies.

B. Clinical endpoints

a) *Primary endpoints*

- The hypothesis regarding the scoring is that patients receiving ORIGIN implants will experience a more natural feel of the prosthesis during the first year after the surgery compared to patients receiving VANGUARD implants (as measured with FJS)

- The primary endpoint of this study is:

- To compare the ability of patients to forget their operated knee at 1 year after the surgery, measured by the Forgotten Joint Score 12 (FJS-12 Knee).
- To compare patient satisfaction regarding the surgery with a CE marked custom-made implant (ORIGIN®) versus off-the-shelf (VANGUARD PS) device. A short self-reported questionnaire[3] will be used.

b) *Secondary endpoints will evaluate clinical performance and safety of ORIGIN System:*

- Secondary endpoints:
  - Evaluate the success of the procedure
  - Evaluate surgeon satisfaction regarding the use of implants and instruments
  - Evaluate outcomes: complications & revision rate with the ORIGIN SYSTEM at the last (2y) follow-up visit
  - To compare the PROMs between the two groups at 1y follow-up and 2y follow-up visits.
  - Evaluate performance of the ORIGIN System vs VANGUARD PS at 2 years follow-up: clinical examination and scoring.
  - To evaluate/compare the clinical, functional and quality of life outcomes using the following four scores:
    - Clinical examination
    - The Knee Injury and Osteoarthritis Outcome Score (KOOS)
    - The Oxford Knee Score (OKS)
    - The EQ-5D-5L Score
    - A self-administrated patient satisfaction questionnaire.
  - To evaluate/compare the clinical, functional and quality of life outcomes with the following surgeon reported scores:
    - The Knee Society Score (KSS) (Objective Knee Indicators only)
    - Knee Society Radiographic Evaluation and Scoring System (KSRESS)
    - The Single Leg Stance Test (SLS)
    - The Timed Up & Go test (TUG)
  - Radiological evaluation:
    - X-rays: AP, lateral, sunrise, long leg weight bearing film
    - Femoral patellar arthrosis: Iwano classification (stage 1 mild to 4 very severe),
    - KRESS Radiological assessment: Patellar tilt angle, patellar displacement, tibial slope, anatomical axis (angles α – β), mechanical axis, (HKA angle, F angle, T angle, HKS angle)
    - Evaluate the radiographic limb alignment, radiolucent lines and radiographic loosening (according to the "Modern Knee Society Radiographic Evaluation System and Methodology for Total Knee Arthroplasty" version 2015)

[3] The self-administered patient satisfaction scale for primary hip and knee arthroplasty. N. Mahomed,1 Rajiv Gandhi,1 Lawrence Daltroy,2 and J. N. Katz3
doi:10.1155/2011/591253

Endpoints evaluation is based on a significant improvement between preoperative & last follow-up at two years.

C. Hypothesis

The hypothesis regarding the scoring is that patients receiving ORIGIN implants will experience a more natural feel of the prosthesis during the first year after the surgery compared to patients receiving VANGUARD implants (as measured with FJS), and slightly significant improvement at the following interval of 2 years. The overall patient satisfaction is expected to be improved after 2 years follow-up. It is also supposed that the overall patient satisfaction is expected to be 13.4 points higher with ORIGIN PS than with VANGUARD PS treatment. (Cf. Chapter Statistical Analysis. Section A. Sample size calculation)

D. Anticipated adverse events assessment

Adverse effects of the ORIGIN® knee prosthesis are similar to other total knee prostheses on the market.

The expected anticipated adverse events in knee replacement surgery are:

- Displacement and loosening (wear, lysis) of the prosthesis
- Patellar component dislocation, tibial insert component disassociation, femorotibial luxation instability, malalignment, malposition
- Pain, stiffness
- Infection
- Venous thrombosis and pulmonary embolism
- Cardiovascular disorders
- Hematoma
- Delayed wound healing
- Grating sounds in the friction pairs, clicking sensation between post-cam (Tibia Insert plot and Femoral cam), soft tissue impingement, patellar component clunk syndrome
- Implant breakage
- Periprosthetic fracture
- Other effects not known to date or not scientifically established

The list of reportable adverse events in the Adverse Event Form is in explained in the XVI.ADVERSE EVENTS, ADVERSE DEVICE EFFECTS AND DEVICE DEFICIENCIES.

The following list of safety outcomes should be collected in the eCRF case report form which will trigger a notification to Symbios regulatory department via regulatory@symbios.ch:

- Serious Adverse Events (SAEs)
- Unanticipated Adverse Device Effects (UADEs)
- Devices deficiencies
- Non-serious Adverse Events related to the device or study procedure
- Secondary surgical procedures or revisions
- Surgical complications

VII. DESIGN OF THE CLINICAL INVESTIGATION PLAN

A. Study description

This is a prospective, comparative, randomized, double arm, monocentric, observational, post-market study. The study is performed in Germany, in the University Medical Center of Johannes Gutenberg-University Mainz (UMC- Mainz).

It is stated that 140 subjects implanted with either the ORIGIN PS or VANGUARD PS System will be included upon eligibility assessment. Subjects will be followed at one and two years after the procedure. The clinical assessment is presented in Chapter XXI APPENDICES.

Enrollment will occur at the time of the medical examination. It is assumed that the subjects' treatments and follow-up visits will be performed per standard of the investigational site in Germany.

It is anticipated that enrollment will take approximately 18 months. As each implanted subject is to be followed for two years, the estimated study duration is approximately 48 months, excluding the time required for preparing the final report. (A loss of approximately 10% is expected at the end of the study)

B. Completion of the Clinical Investigation

The completion of a clinical investigation will coincide with the last visit of the last subject (supposed to be after 2 years follow-up visit:

- First patient in: JAN 2021
- Last patient in: JUNE 2022
- And when follow-up is complete for the clinical investigation, expected completion in JUNE 2024 (last patient last visit)
- Study closure: expected approximate date: OCT-2024

Except if the clinical investigation is terminated prematurely. (Cf. Chapter XVII EARLY TERMINATION OR SUSPENSION OF THE STUDY)

The Final Report will be prepared when all patients complete their follow-up evaluations. It will also be written after collected data are verified, cleaned, and after the eCRF is complete for data analysis.

C. Randomization

There are three major identified barriers for randomized clinical trials on medical devices, namely: (1) randomization, including timing of assessment, acceptability, blinding, choice of the comparator group and considerations on the learning curve; (2) difficulties in determining appropriate outcomes; and (3)

the lack of scientific advice, regulations and transparency.[4] In order to build a powerful clinical study, randomization will be applied and patients will receive equal information regarding both prostheses treatment. The randomization procedure will be unpredictable so that investigators cannot guess the next subject's group assignment based on prior treatment assignments. The study will not be blinded, anyhow all attempt will be chosen to prevent bias regarding PROMs data collection and surgeon reported scores.

The study is a randomized trial with two arms:

- Arm 1/ Device under evaluation: Group of 70 subjects who will undergo a surgery with the ORIGIN PS System
- Arm 2/Comparative device: Group of 70 subjects who will undergo a surgery with the VANGUARD System Cf. CHAPTER. XXI. APPENDICES C. RANDOMIZATION FLOW CHART

The randomization will be performed via a secure unique comprehensive eHealth platform named Bepatient which will be used for the purpose of this study, as a live electronic case report form or eCRF. Additional data are displayed in Section XXI. APPENDICES. F. BEPATIENT DATA HANDLING

Bepatient eCRF ensures the respect of the compliance with good practices (21 CFR part 11) and in accordance with the General Data Protection Regulation (GDPR). Authorized site personnel as indicated on the Delegation Task List, will be trained on the use of the system and will be provided with a username and password to access the system in a limited and secure way. CRFs will be implemented to capture the data for each enrolled subject as required by the protocol.

The study methods include the following measures to minimize potential sources of bias:

- The enrolment is controlled and tracked in the eCRF (external partner) to avoid introduction of bias in the trial
- A dedicated Vigilance department will review all deaths and safety endpoint related adverse events
- The site will follow-up a standardized protocol for acquisition of endpoints data in the eCRF.
- Study site will ensure patients are well informed regarding both prosthesis treatment, to avoid introduction of bias in the questionnaire completion. Site will follow their own procedures regarding the execution of the study, in their facilities (eg. Radiological evaluation), involving nurses and clinical trial team in the clinical assessment, when appropriate to avoid bias of data collection.
- Study monitors will verify patients' data and ensure compliance with the Clinical Investigational Plan and other study requirements.

[4] https://www.nweurope.eu/media/3231/specific-barriers-to-the-conduct-of-randomised-clinical-trials-on-medical-devices.pdf

D. Investigational device(s) and comparator(s)

a) *Description of exposure to ORIGIN & VANGUARD*

ORIGIN® PS and VANGUARD® PS as compared total knee prostheses.

Name	ORIGIN® PS	VANGUARD® PS
Manufacturer	SYMBIOS Orthopédie SA	ZIMMER BIOMET
Type	Bi/tri compartmental	Bi/tri compartmental
Cinematic	Postero-stabilized	Postero-stabilized
Bearing	Fixed	Fixed
Femoral component		
Name	ORIGIN® PS Femur Cemented	Vanguard PS Closed Box Interlok stem
Material	CrCo	CrCo
Sizes	Patient-specific	10
Fixation	Cemented	Cemented
Tibial insert		
Name	ORIGIN® PS Insert	Vanguard PS Tib Bearing
Material	Standard polyethylene	Antioxidant polyethylene E1
Sizes	Patient-specific	5
Thickness	6 or 8 mm	10 to 24 mm (2 mm increments)
Tibial tray		
Name	ORIGIN® PS Tibia Cemented	CoCr Finned Tibial Tray
Material	Titanium	CrCo
Sizes	Patient-specific	9
Symmetry	Asymmetric	Symmetric
Fixation	Cemented	Cemented
Patellar component		
Name	ORIGIN Patella Cemented	Serie A Patella
Material	Polyethylene	Polyethylene
Instruments		
Cutting	KNEE-PLAN® Guides ORIGIN®	Conventional cutting guides
Other instruments	KNEE-PLAN® Set ORIGIN®	Standard instrumentation
Pre-operative planning		
Type	3D CT-Based with KNEE-PLAN®	2D X-rays[5]

According to regular clinical practice, x-rays (standing long leg, ap, lateral, patella sunrise views) are taken for all patients preoperatively as well as a planning CT-scan of hip, knee and ankle for patients randomized to the Origin group.

[5] Long leg, knee in 2 planes and patella sunrise

b) *Discussion of implant's risks, pros and cons*

Standard TKA implants are off-the-shelf and therefore only come in a certain number and range of sizes. Manufacturers aim to provide solutions for most patients with a limited number of implants. Essential interindividual differences have been shown to exist regarding the size of the femoral condyles, trochlear morphology and geometry of the tibial plateau (Steiner AF et al. Orthopade 2016). To accommodate for a patient's individual anatomy, a surgeon must therefore find the best fit option for each patient which when using OTS implants in some cases means to compromise between implant rotation, fit and bony coverage. Since femoral overhang and tibial malrotation have been linked with persistent postoperative pain (Mahoney OM et al. J Bone Joint Surg 2010; Nicoll D et al. J Bone Joint Surg Br 2010) these compromises might lead to dissatisfaction after TKA surgery. With a custom implant recreating a patient's individual anatomy said compromises shouldn't be necessary anymore, possibly resulting in a higher patient satisfaction.
While younger, more active patients profit from more normal kinematics as outlined in the introduction, custom implants hold potential benefits for elderly patients as well. Osteoporotic bone is a common problem in this age cohort and to avoid subsidence surgeon's aim for cortical coverage of the tibial base plate. While this can easily be achieved with a CIM TKA, the same is difficult and sometimes impossible with OTS TKA.

While the individuality of CIM implants leads to the upsides mentioned above, the manufacturing process of individual knee implants is inherently different from the one of OTS implants. A CT scan needs to be done to compute a 3D model of a patient's knee according to which the final implants will be produced within a 6 to 8 week timeframe. One might argue this waiting period is to a disadvantage for patients randomized into the CIM TKA group, but in our experience the waiting period for this type of elective orthopedic surgery is approximately 6 to 8 weeks anyways.

Another possible downside of CIM implants arises in the case of an early periprosthetic infection. Following the DAIR (debridement, antibiotics and implant retention) approach, inserts should be exchanged during revision surgery. While new inserts for OTS implants are usually on stock, this might not be the case for CIM inserts. From our point of view this can be handled by requesting a replacement insert from the manufacturer. If the patient needs emergency surgery, leftover inserts kept from his primary surgery can be used until this replacement is available.

E. Study population

The study population includes patients suffering from non-inflammatory degenerative and inflammatory knee joint disease and for who no alternative treatments are possible.
It anyhow includes patients who have provided consent to participate in the study. Patients who have met the protocol eligibility criteria will be enrolled into the prospective study.

Pediatric, legally incompetent, or otherwise vulnerable patients are not eligible for the study.

F. Inclusion criteria

It is planned to include consecutive eligible subjects which will be randomized to Arm 1: ORIGIN SYSTEM or Arm 2: VANGUARD system. Subjects will be enrolled upon evaluation via a clinical examination at the preoperative stage. Subjects should meet the following criteria:

- Male and female over 18 years of age.
- Each patient, or his or her guardian or legal representative, is willing to give informed consent.
- Clinically indicated for a total Knee replacement
- Females who are not pregnant or lactating and not planning to become pregnant ≤ 12 months. A pregnancy test may be performed to confirm this
- Geographically stable and willing to return to the implanting site for all follow-up visits.

G. Exclusion criteria

Patients meeting any one of the following criteria will be excluded from participating in this study:

- Life expectancy ≤ 1 year
- Age ≥ 80 years
- Acute or chronic, local or systemic infection
- Mental illness
- Muscular, ligamental, neurological, psychological or vascular deficits
- Bone destruction or poor bone quality likely to affect implant stability (requiring a femoral and/or a tibial stem and/or a thick insert)
- Any concomitant condition likely to affect implant integration or function
- Allergy or hypersensitivity to any of the materials used
- For devices in CoCrMo (ISO 5832/4): renal and hepatic impairment
- Hip Knee Ankle (HKA) angle < 165° or > 195°
- Severe collateral ligaments deficiency (requiring a more constrained prosthesis)
- Major anatomical deformities
- Severe flexion contracture or severe recurvatum
- Revision of a partial or total knee prosthesis
- Non-extractible material (e.g. screws, plate, intramedullary nail, osteosynthesis material…) which can create a conflict with any component of the prosthesis
- Distal and/or posterior and/or anterior femoral bone loss which exceeds the femoral component thickness
- Proximal tibial bone loss which exceeds the tibial component thickness (tibial tray + tibial insert)
- Allergy of any implant material

H. Criteria and procedures of subject withdrawal or lost to follow-up

a) *Missed Follow-up Visit*

The Investigator should make every effort to contact the subject preferably within the visit window, to collect the subject's vital status as well as information related to potential adverse events, safety data, and hospitalizations.
As only standard of care data are being collected, subjects cannot miss study-specific visits. In case no standard of care visit has taken place in the pre-specified follow-up interval period, sites should conduct a telephone follow-up visit just prior to the closure of the visit window. Up to 2 attempts and any information received during a telephone follow-up should be filed as source documentation by the sites.
If the subject cannot be reached by phone, the visit should be considered missed and, if applicable a protocol deviation must be completed, as outlined in chapter XII. DEVIATION FROM THE CLINICAL INVESTIGATION PLAN.
A replacement of withdrawn or discontinued subjects in the study is not planned. Therefore, these subjects will be documented as lost-to-follow-up in the source documentation.

b) *Lost to Follow-Up*

The subject may only be considered lost to follow-up after all efforts to obtain compliance are exhausted. At a minimum, three attempts must be made to contact the subject and documented in the subject's trial records:
• 2 telephone attempts to the subject's last known phone number, and if unsuccessful,
• 1 certified letter from the PI to the subject's last known address
If the site is unable to reach the subject after the documented attempts, the site should make every attempt to verify the subject's vital status (alive or deceased). Should the participant continue to be unreachable, he or she will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

c) *Subject Withdrawal*

All subjects will be encouraged to remain in the study through the last follow-up visit at two years. Subjects who discontinue participation prematurely will be included in the analysis of results (as appropriate) but they will not be replaced in the enrollment of total study subjects. If a study subject is discontinued from the study early, the reason for discontinuation should be documented in the subject file and a Study Exit e-CRF must be completed. If discontinuation is because of safety or lack of effectiveness, the patient shall be asked to be followed for collecting safety data outside the clinical study.
Once a subject has been enrolled in the study (i.e. written Informed Consent has been obtained) he/she may withdraw his/her consent to participate in the study at any time without prejudice. Participation in this study is entirely voluntary.
If a subject discontinues the study at any time, is withdrawn from the study early, or completes all follow-up visits they should continue to be followed by the implanting center according to their standard clinical practice.

I. The point of enrolment

Potential subjects are identified by the Investigator or study staff based on patients' clinical and radiographic assessments during regular medical care.
The point of enrolment could be during the preoperative visit, or even earlier. The enrolment is effective and complete upon patient's signature on the approved informed consent form and after the patient has been informed of participating in the study. The Investigator or study staff provides study information and the approved Informed Consent Form (ICF) to potential subjects and answers any questions during the preoperative clinic visit. In order to provide adequate time for consideration, potential subjects will take study information and ICF home with them. When an informed decision has been made (minimum consideration time 24 hours) ICFs are returned either in person or via facsimile. Any ICFs transferred via facsimile must be returned in their original version prior to surgery. A copy of the ICF will be handed over to the patient, the signed original version will be kept and traced in the patient file.

Once the patient signs the consent form, he/she is considered as enrolled in the study and will be randomized into one of the two treatment groups: ARM 1: ORIGIN PS system or ARM 2: VANGUARD PS System right after eligibility assessment about 6 to 8 weeks prior to surgery. The randomization will automatically generate a unique subject identification code which will be used through the study participation. The institution site shall keep a log of recruited subjects based on inclusion or exclusion criteria (full name, trial number, and hospital or practice identification number), in the subject identification Log.

J. Study duration

It is anticipated that enrollment will be completed within 18 months. As each implanted subject is to be followed for two years, the estimated study duration is approximately 48 months, excluding the time required for preparing the final report. The study is considered to have ended on the date of the final visit by the final trial subject (Last patient last visit).

VIII. PROCEDURES

A. Overview

Assess patient satisfaction regarding the surgery with a custom-made implant (ORIGIN®) versus off-the-shelf (VANGUARD PS) device.

Document the clinical and device performance outcomes of ORIGIN SYSTEM used in routine hospital practice in a large patient cohort for the treatment of total knee replacement (TKR).
No additional radiological, clinical, or biological exams, compared to routine practice.

Evaluation of the performance and the safety of the ORIGIN® knee prosthesis and of the KNEE-PLAN® ORIGIN® instruments. The subjects will be treated either with the ORIGIN System or with VANGUARD PS and will be included upon eligibility assessment. Subjects will be followed at 1 and 2 years after the procedure. Study data will be recorded in the Case Report Form (Cf. APPENDICES) via an electronic platform.

B. Investigator Site selection

The role of the principal investigator is to implement and manage the day-to-day conduct of the clinical study as well as ensure data integrity and the rights, safety and well-being of the subjects involved in the clinical study.

An investigator may be included in the clinical study if compliant with the following requirements:

- Qualified surgeon legally entitled to practice
- Experienced in the diagnosis and treatment of patients requiring a total knee replacement with ORIGIN or VANGUARD systems
- Experienced with at least 10 cumulative ORIGIN and VANGUARD implantations
- The Principal Investigator has demonstrated experience with conducting clinical (device) trials that comply with applicable regulatory standards
- Principal Investigator, co-investigators, and study staff must be willing to provide their Curriculum Vitae and training evidence

C. Clinical Investigation Agreement

A Clinical Investigation Agreement should be in place, signed by the participating investigation site and/or principal investigator of each investigation site, as per the local legal requirements, and returned to Symbios prior to the commencement of any clinical study activities. The investigator is indicating approval of the CIP and subsequent amendments, by a fully executed agreement. The agreement is separately issued and is based on the CIP requirements.

D. EC approval

Prior to enrolling subjects in this clinical study, the local German EC will be required to approve the current Clinical Investigation Plan, the Patient Informed Consent form,. EC approval of the clinical study must be received in the form of a letter and provided to Symbios before commencement of the clinical study at an investigation site.

Competent Authorities (BfArM) submission is not required since both evaluated devices are CE marked and are being used within their indication for use.

The approval letter must contain enough information to identify the version or date of the documents approved. If this information is not contained in the approval letter, it must be retrievable from the corresponding submission letter.

E. Study site initiation

After the EC approval is obtained, a joined Site Initiation Visit will be planned at the investigational site. A list of participating team members should be completed and maintained during the course of the Study. New personnel should only start their assignment after receiving adequate training in the clinical investigation requirements and this training shall be documented. The names, initials, signatures, functions, and designated authorizations of new personnel shall be documented.

The purpose of this visit is to provide training to the Study staff including the following items:

- Clinical Investigation Plan and execution
- Training on the device under investigation
- Training on the eCRF by the sponsor or its representative (bepatient)
- Regulatory requirements, and Investigator responsibility training provided by the sponsor or its representative (CRA TRIUM)
- Study documentations and Investigator Site File (ISF)
- Other if applicable for the correct execution of the study.

The study staff will complete a training log, to assess date of training and completion of the site initiation visit. This log will be provided by the sponsor and kept, on site, in the ISF.

F. Description of all clinical investigation related subject procedures

a) *Preoperative data*

There are established visit windows defined in this study based on standard clinical practice (Cf. XXI.APPENDICES. B. SCHEDULE OF ASSESSMENT).

During the preoperative visit, the following baseline data will be collected:

- Subject Information or consent (at least 24h prior to the preoperative visit) – Date of consent

- If consent obtained, date of preoperative visit (DD/MM/YYY)
- Date of randomization and Arm attribution Group 1 (ORIGIN) or 2 (VANGUARD)
- Inclusion/exclusion criteria
- Demographic data:
  - Gender: Male, female
  - Year of birth, (DD/MM/YYYY)
  - Age of patient: (YY)
  - Weight, (between 20 and 250Kg)
  - Height, (between 80 and 250cm)
  - BMI (kg/m^2)
- Indication : Severe painful and/or disabled knee joint, resulting from:
  - Non-inflammatory degenerative knee joint disease
  - Osteoarthritis, necrosis, post traumatic arthritis

  Or Inflammatory knee joint disease:

  Rheumatoid arthritis
- Medical Knee history
  - number of previous knee surgeries
  - description of knee surgeries: medial meniscectomy, lateral meniscectomy, arthroscopy, tibial/femoral osteotomy, other to specify
- Radiological examination
  - If patient is assigned to Arm 1: Pre-op CT Scan will be performed for the design of the ORIGIN prosthesis. Pre-op RX will be performed as well per standard of care
  - If patient is assigned to Arm 2: Pre-op RX[6] will be performed for the implementation of the VANGUARD PS system. (AP, lateral, sunrise)
- Surgeon reported scores:
  - KSS score (Objective Knee Indicators only)
  - X-rays: AP, lateral, sunrise, long leg weight bearing film
  - Femoral patellar arthrosis (Iwano classification (stage 1 mild to 4 very severe)),
  - Knee Society Radiographic Evaluation and Scoring System (KSRESS): patellar tilt angle, patellar displacement, tibial slope, anatomical axis (angles $\alpha - \beta$), mechanical axis (HKA angle, F angle, T angle, HKS angle)
  - Single Leg Stance test (SLS)
  - Timed up and go (TUG)
- Patient reported scores:
  - KOOS Score
  - OKS Score
  - FJS Score
  - EQ-5D-5L Score
  - A self-administrated patient satisfaction questionnaire.

[6] Long leg, knee in 2 planes and patella sunrise

b) *Perioperative data*

1. Surgery procedure

The Surgery procedure is performed according to the standard procedures of the surgeon at the hospital. The surgical approach should be performed according the Instruction for Use of the ORIGIN System. Regarding VANGUARD, the operative technique is in accordance with the surgical technique guide provided by Biomet. Surgery will be performed or supervised by an experienced orthopedic surgeon.

The following data will be collected:

- Date of surgery (DD/MM/YYYY)
- Surgeon name (First and Last name)
- Implanted side (L/R)
- Approach (medial/lateral)
- Implanted device: ORIGIN PS (Monobloc or Modular) vs VANGUARD PS
- Reference & Lot number of the implanted devices if ORIGIN PS System
- Reference & Lot of the associated used instruments if ORIGIN System
- Surgery total duration time (skin-to-skin) for both Arms
- Safety evaluation for ORIGIN System & VANGUARD PS:
    - Perioperative complications
    - Perioperative difficulties
    - Surgeon satisfaction regarding devices and instruments for ORIGIN PS System (via surgeon satisfaction form)
    - Femoral and tibial sizing, patellar resurfacing

- Surgeon satisfaction: during surgery, the surgeon will assess safety and performance of the listed Instruments in the Chapter XXI.APPENDICES. These data will be collected in the case report form based on surgeon satisfaction and will be used in clinical evaluation of Symbios ORIGIN PS System.

Surgeon satisfaction during surgery regarding ORIGIN IMPLANTS:

CRITERIA OF EVALUATION	SURGEON IMPLANTS SATISFACTION	
EVALUATION OF CUTTING GUIDES	□ ☺ □ ☹	
	□ *if unsatisfied, please specify* -	□ *Femoral cutting guide* □ *Tibial cutting guide* □ *Recut guide* □ *4 in 1 guide* □ *Intercondylar notch*
COVERAGE OF FEMORAL & TIBIAL COMPONENT	□ ☺ □ ☹	
	□ *if unsatisfied, please specify:*	□ *Femoral component* □ *Tibial component*
TIBIAL RECUT	□ *Yes* □ *No* *If yes, please specify : □1mm / □2mm / □3mm / □4mm*	
JOINT BALANCING	*0°*	□ ☺ □ ☹
	30°	□ ☺ □ ☹
	90°	□ ☺ □ ☹
	120°	□ ☺ □ ☹
PATELLA RESURFACING *(if applicable)*	□ Yes □ No	
LATERAL FACETECTOMY	□ Yes □ No	
LATERAL RELEASE	□ Yes □ No	
Modular Stem	□ Yes □ No *If yes, please specify : □20mm / □30mm / □40mm / □70mm*	
OVERALL GLOBAL SURGEON SATISFACTION	□ ☺ □ ☹	

Surgeon satisfaction during surgery regarding ORIGIN INSTRUMENTS

SURGICAL STEPS	INSTRUMENTS SATISFACTION
DISTAL FEMORAL CUT	□ ☺ □ ☹ □ if unsatisfied, *(Please specify name of instrument related to the comment):* _____
A/P FEMORAL CUTS AND CHAMFER CUTS	□ ☺ □ ☹ □ if unsatisfied, *(Please specify name of instrument related to the comment):* _____
INTERCONDYLAR CUTS	□ ☺ □ ☹ □ if unsatisfied, *(Please specify name of instrument related to the comment):* _____
FEMUR TRIAL-EVALUATION OF THE DEFORMATION	□ ☺ □ ☹ □ if unsatisfied, *(Please specify name of instrument related to the comment):* _____
PROXIMAL TIBIAL PRE CUT	□ ☺ □ ☹ □ if unsatisfied, *(Please specify name of instrument related to the comment):* _____
PRE-TRIALS AND TIBIAL CUT ADJUSTMENT	□ ☺ □ ☹ □ if unsatisfied, *(Please specify name of instrument related to the comment):* _____
TIBIAL BASE PLATE PREPARATION	□ ☺ □ ☹ □ if unsatisfied, *(Please specify name of instrument related to the comment):* _____
FINAL TRIALS	□ ☺ □ ☹ □ if unsatisfied, *(Please specify name of instrument related to the comment):* _____

PATELLAR PREPARATION *(if applicable)*	□ ☺ □ ☹ □ if unsatisfied, *(Please specify name of instrument related to the comment):* _____
IMPLANTATION	□ ☺ □ ☹ □ if unsatisfied, *(Please specify name of instrument related to the comment):* _____

The surgeon will assess safety and performance of the listed Instruments in the Chapter XXI.APPENDICES. LIST OF INSTRUMENTS

2. *Attempted procedure*

An attempted procedure is one where:

- The patient has been randomized to ORIGIN arm but won't receive the prosthesis (neither the VANGUARD) because the 3D preoperative planning of the design has shown shape incompatibilities or abnormalities.
- The study subject has entered the procedure room for implantation but did not receive an ORIGIN implant for any reason. (Implants broken or defective, use of another implant VANGUARD excluded in that case)

If a procedure was attempted, and the ORIGIN is not implanted, the subject will be followed for safety reporting for 30 days post-attempted implant, and then exited from the study. Adverse Events data should be collected on the AE e-CRF.

c) *Follow-up data at 1-year visit*

There is an established visit window defined in this study, the following postoperative follow-up data will be collected at 12M (1 year).
The follow-up window is flexible and is set as a guidance to +/-1M for the first visit at 1 year.

The following data will be collected in the eCRF:

- Date of visit (DD/MM/YYYY)
- Name of Surgeon
- Physical examination
  - Weight, (between 20 and 250Kg)
  - Height, (between 80 and 250cm)
  - BMI (kg/m²)
- Radiological examination per standard of care (ap, lateral, sunrise)-
- Femoral patellar arthrosis (applicable if it is an anatomic patella not a prosthetic implant), patellar tilt angle, patellar displacement, tibial slope, femoral component flexion, anatomical axis (α angle, β angle), mechanical axis (HKA angle, F angle, T angle, HKS angle)

- Surgeon reported scores will be collected during this visit:
  - The Knee Society Score (KSS) (Objective Knee Indicators only)
  - Knee Society Radiographic Evaluation and Scoring System (KSRESS)
  - Single Leg Stance Test or (SLS)
  - Timed up and go (TUG)
- Evaluate radiographic loosening (according to the "Modern Knee Society Radiographic Evaluation System and Methodology for Total Knee Arthroplasty" version 2015)
- Radiolucent lines; Femur,frontal Tibia frontal, Tibia profil, Patella

- Satisfaction of the patient based on performance evaluation of the evaluated device ORIGIN vs VANGUARD based on scoring via FJS questionnaire:
  - FJS score
  - A self-administrated patient satisfaction questionnaire. (3 questions)

The hypothesis regarding the scoring is that patients receiving ORIGIN implants will experience a more natural feel of the prosthesis during the first year after the surgery compared to patients receiving VANGUARD implants (as measured with FJS).

The overall patient satisfaction is expected to be improved after 1-year follow-up for ORIGIN vs VANGUARD.

FJS score at the postoperative visits will be collected per standard of care at the investigational site.

- Evaluate performance of the ORIGIN System vs VANGUARD PS at 1-year follow-up: clinical examination, and scoring. To evaluate/compare the clinical, functional and quality of life outcomes with the following scores:
  - The Knee Injury and Osteoarthritis Outcome Score (KOOS)
  - The Oxford Knee Score (OKS)
  - The EQ-5D-5L Score

- Safety evaluation of the implanted device ORIGIN:
  - Evaluation of Complications using the adverse event form (Cf. Adverse events form in XXI APPENDICES)
  - Evaluation of Revisions (It is also required to complete an AE form in case of revisions)
  - Global revision rate not higher (Interval 95%: p>0.05) than the state of the art.

d) *Follow-up data at 2 years visit*

There is an established visit window defined in this study, the following postoperative follow-up data will be collected at 24 M (2 years)
It is assumed that the visits will be planned per standard of care. (Window set at +/- 2 month).

The following data will be collected in the eCRF:

- Date of visit (DD/MM/YYYY)

- Name of Surgeon
- Physical examination
    - Weight, (between 20 and 250Kg)
    - Height, (between 80 and 250cm)
    - BMI (kg/m²)
- Radiological examination per standard of care (ap, lateral, sunrise)- -
- Femoral patellar arthrosis, (applicable if it is an anatomic patella not a prosthetic implant), patellar tilt angle, patellar displacement, tibial slope, femoral component flexion, anatomical axis (α and β angles), mechanical axis (HKA angle, F angle, T, angle, HKS angle)
- Surgeon reported scores will be collected during this visit:
    - KSRESS
    - Single Leg Stance Test or (SLS)
    - Timed up and go (TUG)

- Evaluate the radiolucent lines and radiographic loosening (according to the "Modern Knee Society Radiographic Evaluation System and Methodology for Total Knee Arthroplasty" version 2015) - Radiolucent lines; Femur frontal, Tibia frontal, Tibia profil, Patella

- Satisfaction of the patient based on performance evaluation of the evaluated device ORIGIN vs VANGUARD based on scoring via FJS questionnaire:
    - FJS score
    - A self-administrated patient satisfaction questionnaire.

The hypothesis regarding the scoring is that patients receiving ORIGIN implants will experience a more natural feel of the prosthesis during the first year after the surgery compared to patients receiving VANGUARD implants (as measured with FJS)

The overall patient satisfaction is expected to be improved after 2 years follow-up for ORIGIN vs VANGUARD.
FJS score at the postoperative visits will be collected per standard of care at the investigational site.

- Evaluate performance of the ORIGIN System vs VANGUARD PS at 2 years follow-up: clinical examination, and scoring. To evaluate/compare the clinical, functional and quality of life outcomes with the following scores:
    - The Knee Injury and Osteoarthritis Outcome Score (KOOS)
    - The Oxford Knee Score (OKS)
    - The EQ-5D-5L Score

- Safety evaluation of the implanted device ORIGIN:
    - Evaluation of Complications using the adverse event form (Cf. Adverse events form in XXI: APPENDICES)
    - Evaluation of Revisions for both Arms (It is also required to complete an AE form in case of revisions)
    - Global revision rate not higher (Interval 95%: p>0.05) than the state of the art.

e) *Scores*

Cf. Forgotten Joint score (FJS) – Chapter XXI. APPENDICES. E. PATIENT SELF-QUESTIONNAIRE

The Forgotten Joint Score (FJS) is a joint-specific questionnaire developed in 2012 (Behrend et al. 2012) with the aim to measure PRO of joint disorders (Hamilton et al. 2017). FJS is designed to measure the ability of the patient to "forget" about their problematic joint after treatment. FJS is available in 3 versions: hip, knee, and shoulder.[7] In the following editorial: *The Forgotten Joint Scored Don't Compare Apples to Oranges," T*he Forgotten Joint Score asks the simple question, "Are you aware of the joint that had surgery?" Essentially, does the patient have any sense that there has been surgery on the limb or joint? Although it has been validated as a reliable testing technique in specific surgical procedures, it has not been validated as a method of comparing 2 dissimilar surgical procedures." This is why this score will only be used to compare patient satisfaction while undergoing a surgery with ORIGIN or with VANGUARD systems.

FJS is defined in 12 questions:
- Functional outcome, pain, stability and daily living …but additional
- Activity and Sport

The outcome Score is between 0-4. Zero is best outcome. Low score means high satisfaction.
All responses are summed and multiplied by 25 (Total= 0-100)

Overall patient satisfaction will therefore be calculated based on patients PROMs. (Patient reported outcome measures) This score will be used to evaluate patient satisfaction with ORIGIN vs VANGUARD which should lead to a higher score (>13.4 points)

G. Description of monitoring activities

a) *Monitoring*

Monitoring visits will be conducted during the enrolment, follow-up and close out study phases in accordance with Symbios / TRIUM SOPs and the Monitoring Plan. The purpose of monitoring of the study is to verify compliance with the clinical protocol, the EU Regulation and ISO 14155. It will be conducted by an independent qualified monitor or CRA (TRIUM, external partner or CRO). Monitoring oversight will be provided by Symbios. 100% of the Informed Consents will be reviewed for accurate completion.

eCRF data related to the primary and secondary endpoints as well as study-specific adverse events will be verified against the patient's medical records.

[7] 10.1080/17453674.2019.1599252 (Evaluation of Forgotten Joint Score in total hip arthroplasty with Oxford Hip Score as reference standard)

Site personnel will complete e-CRFs following each subject visit. Study data submitted will be reviewed against patient files and sources containing original records of patient data. Source document verification will occur in accordance with the Monitoring Plan.

The progress of the study will be monitored by:
• On-site review, as deemed appropriate by TRIUM CRA
• Telephone communications between the site personnel (e.g., investigator, study coordinator) and study monitor
• Review of e-CRFs and the associated clinical records
• Review of regulatory documents
• Review of ISF content

The Principal Investigator will permit direct access to study monitors and appropriate regulatory authorities to the study data, to the corresponding source documentations in order to verify the accuracy of these data.

b) *Accessibility of investigation site staff and study materials*

The principal investigator(s), his/her delegate(s) and the study coordinator(s) shall be accessible to Symbios Clinical Study Manager and/or to the monitor or to Symbios representative. This accessibility is of particular importance for reviewing data in the electronic Case Report Form (CRF). Direct access to patient medical files for source data verification will need to be granted and prepared prior to any monitoring visits.

c) *Audits and investigation site inspections*

In addition to regular monitoring visits, Symbios may conduct audits at participating investigation site. The purpose of an audit is to verify the adequate performance of the clinical study related activities. Regulatory bodies may also perform inspections at participating investigation site. Any regulatory authority inspection announcements shall be forwarded immediately to the Clinical Affairs Manager.
The investigator and/or institution shall permit Symbios and regulatory bodies direct access to source data and documents, taking into account any restrictions due to local law, to perform clinical study-related monitoring, audits, EC review, and regulatory inspections.

H. Factors that might compromise study interpretation of results

Anticipated factors that could compromise study interpretation of data and a lack overview of clinical data:

- Differences in patient selection that may not be easily documented, which could lead to differences in outcome that are mistakenly attributed to the use of the new device such as ORIGIN
- Higher loss of study population (higher than >10% expected)
- Low quality of data collection (if not study monitoring oversight)

- Traceability and consistency of collected data
- Statistical differences could be in baseline demographics between ORIGIN vs VANGUARD in patient satisfaction, including slightly differences in age, comorbidities and sex.
- Surgeon overall satisfaction regarding both implants ORIGIN and VANGUARD and possible surgical factors who could play a role in the patient outcome or on the performance of the implant
- Heterogeneity in subjects regarding their answers in the FJS self-questionnaire

The choice of investing in a long-term EDC solution to collect and store the data will leverage the full potential of Symbios clinical data in order to mitigate the factors that might compromise study data interpretation and analysis.

IX. MONITORING PLAN

The Monitoring Plan defines the extent and type of the monitoring activities, describes the responsibilities of those involved as well as trial specific aspects and include the Symbios / TRIUM SOPs governing monitoring activities.

Cf. CHAPTER XXI. APPPENDICES. MONITORING PLAN.

X.STATISTICAL ANALYSIS

a) *Sample size*

The size of the two groups depends on several factors which are involved in the hypothesis made (see table 1).
P value is the probability.

Table 1

Table of Error types		H0 is TRUE	H0 is FALSE
Decision aout H0	Don't Reject	Correct, True negative: p=1-α	False negative: p=β type II Error
	Reject	false positive: p= α type I Error	Correct, true positive: p=1- β

Statistical Risk
The standard practice in clinical studies is to set:

- α = 0.05 (5%), this will give us an Interval of confidence of 95%
- β = 0.2 (20%), this will give a power of 80%

Statistical Parameters
In addition to the risk α and β, the Effect Size (ES) must as well as the variance (σ^2) must be known and set.
The ES is the effect product by the difference of treatment between the two groups, in this case it is the MCID calculated previously in section V.A divided by σ (standard deviation).

- ES: $ES = \frac{\mu_1 - \mu_2}{\sigma}$
- σ^2: $\sigma^2 = \frac{1}{n} \cdot \sum_{i=1}^{n} (y_i - \mu)^2$ (with μ, average of population, and x_i a single value)
-

Hypothesis considered
Considering following hypothesis:

- Provided that the studied responses (Y_1 *and* Y_2) are independent variables
- Provided that group size will be larger than 30, so that by the Central Limit Theorem (CLT) can be applied (Y_1 *and* Y_2 normally distributed, Gaussian)
- Provided that the patients (x_{ij}) are randomized
- Provided that σ is equivalent within the two group ($\sigma_1 = \sigma_2$)

Calculation
According to the hypothesis considered, the Z distribution can be used to figure the group size (n):

n: $n = 2/ES^2 \cdot (z_{1-\alpha/2} + z_{1-\beta})^2$

- ES= MDIC/ σ 13.4/26.8=0.5
- $Z_{1-\alpha/2}$=1.96
- $Z_{1-\beta}$=0.84
- ⇨ *n* ≥63 per group.

Lost patient
Typically, the margin of lost patient is within 10% which in our case is rounded to 7 patients per group.

Final figures for group's size

n_1 = 70 patients
n_2 = 70 patients

b) *Patient Reported Outcomes Measures (PROMs)*

The Minimal Clinical Important Difference (MCID) is the minimum difference in Patient Reported Outcomes Measures (PROM) that is meaningful for the patient.

With a distribution-based approach[8], the ability of patient to discriminate each task after the surgery is approximately half a Standard Deviation. Therefore, for the purpose of this study, MCID will be evaluated by half of the Standard Deviation (SD) of the Forgotten Joint Score. (cf. Primary endpoints)

A literature review on the FJS in TKR has been performed (cf. Chapter XX: Bibliography). Literature shows that the SD of the FJS can be evaluated at 26.8 points.
For the purpose of this study, half of the SD is set at 13.4 points for patient satisfaction between Origin versus VANGUARD.

c) *Analysis of clinical data and Safety outcomes*

The rate of serious adverse events (SAE) and Unanticipated Adverse Device Effects (UADEs) during the study will be presented using the proportions of patients experiencing one or more of each SAE and UADE. All serious and non-serious adverse events will be characterized in terms of severity and relatedness to the operative procedure and device. Additionally, the percent of patients requiring one or more secondary surgical procedures relating to the original procedure will be presented. Data will be analyzed for all patients enrolled in this observational study.

d) *Performance outcomes*

The device success will be evaluated via the performance assessment via the overall surgeon and patient satisfaction. Post-operative surgeon overall satisfaction will be assessed via the following answers: very

[8] https://www.ncbi.nlm.nih.gov/pubmed/12719681
Interpretation of changes in health-related quality of life: the remarkable universality of half a standard deviation

satisfied, satisfied, and not satisfied. Post-operative patient satisfaction will be assessed via the FJS, with a marked improvement in the natural feel of the prosthesis during the first year after the surgery, and slightly significant improvement at the following interval of 2 years.
A final report will be prepared when all patients have completed their follow-up evaluation. No interim analysis is planned.

e) *Statistical Methods and Analysis*

All analyses will be described in a Statistical Analysis Plan (SAP) which will be completed prior to analysis. No interim analysis is planned.

Any deviations from this section and/or the Statistical Analysis Plan will be described and justified in the Final Clinical Study Report, as appropriate.

No statistical techniques will be used to impute missing data for continuous or categorical outcomes. If a subject's data are missing for any reason, that subject will not be included in that portion of the analysis. The number of subjects included in each analysis will be reported so that the reader can assess the potential impact of missing data.
Additional (annual) reports providing only descriptive statistics will only be written upon request of the EC/IRB and/or Regulatory Authority, as applicable.

For statistical analysis, patient satisfaction results will be analyzed into the knee awareness as:

- Never
- Almost never
- Seldom
- Sometimes
- Mostly

The subjects that required further procedures or surgeries on their knee in the initial six months were excluded from this analysis. These patients were excluded from analysis because the outcome and satisfaction scores were likely to be highly influenced by the early additional procedure, and the study was not powered to evaluate the revision rates associated with two implants.

Statistical differences could be identified in:

- Baseline demographics between ORIGIN vs VANGUARD in patient satisfaction, including slightly differences in age, comorbidities and sex.
- Surgeon overall satisfaction regarding both implants ORIGIN and VANGUARD and possible surgical factors who could play a role in the patient outcome or on the performance of the implant?
- Demonstrate superiority of ORIGIN over VANGUARD: higher score by 13.4 points based on MCID evaluation of PROMs.
- If a modular stem is used it could impact radiological analysis: radiolucencies for instance and tibial loosening

XI. DATA MANAGEMENT

a) *Data collection in the eCRF*

The eCRF will be designed to ensure that all required data in the protocol are captured.

A Case Report Form (CRF, see Chapter XXI. APPENDICES) will be completed for each subject enrolled into the clinical study. The investigator will review, approve and sign/date each completed CRF; the investigator's signature serving as attestation of his responsibility for ensuring that all clinical data entered on the CRF are complete, accurate and authentic. It will also track any missed, unused, and/or spurious data.

Bepatient EDC platform will be used and is specifically designed for Symbios needs. Bepatient has developed a unique comprehensive eHealth platform which will be used for the purpose of this study. Bepatient electronic system will be used as the sole instrument for the recording and analysis of clinical data related to the safety and efficacy of the investigational device, and respect the compliance with good practices (21 CFR part 11) and in accordance with the General Data Protection Regulation (GDPR). This tool has a Validated system with an access limited to authorized individuals, compliant password policy (unique ID/password combination), eSignature (investigator, data freeze by monitor / data manager), is secure computer-generated, allow time-stamped audit trail and Study records (print option, export module to your tools / CSV / Excel / SAS).

b) *Source documents*

Entered data in the eCRF must be traceable to source documents. Source documentation is defined as the first time the data appear (original records and certified copies of original records) and may include all clinical records, hospital records, procedural reports, autopsy reports, and any other material that contains original information used for study data collection or adverse event reporting.

Data reported on the e-CRFs should be traceable to source documents. Source documents must be available for review by Symbios personnel and/or applicable local EC and will be used for verification of the data reported on the e-CRFs and adjudication of AEs.
Where copies of the original source document as well as print outs of original electronic source documents are retained, these shall be signed and dated by a member of the investigation site team with a statement that it is a true reproduction of the original source document.
The Investigator must ensure the availability of source documents from which the information on the e-CRFs was derived. In addition, the medical records of study subjects should be marked or flagged in such a way to indicate their participation in the study.

c) *Data management*

A validated database mentioned above will be in place to store the clinical data information.

Once created, it will require a validation of the protocol specific implementation of the EDC. This will be done by Symbios in collaboration with Bepatient prior to the study start.

The Data Management process regarding the data in the eCRF will include all activities related to data handling regarding:

- Data entry & processing (the data will be entered by the appropriate site personnel, listed on the Delegation Task List)
- Data security (the access to the database is secure and based on log in & password details, not accessible to an unauthorized person or individual)
- Data Validation (will ensure the most accurate validated set of data is provided for statistical analysis)
- Data controlling (via a monitor who will verify the accuracy of data entry. Completeness will be checked by authorized personnel at Symbios so that there are no unexplainable empty fields in the eCRF. This is done in order to prevent that data being overlooked by personnel entering the data).
- Database lock (quality control will be performed by the designed Data Manager in order to verify completeness). If the data is validated and no more outstanding queries or discrepancies, the data can be considered as cleaned. At this stage, the database will be locked.

In addition to the above, obvious writing and spelling errors in the eCRF may be corrected without issuing a query.
All comments have to be written in English. Any translation in the CRF should be signed and dated by the investigator.

After receipt of an Adverse Event (AE), the following must be checked immediately:

- Serious Y/N;
- Relationship to procedure/investigational product.

All decisions on the evaluability of the data from each individual subject for the statistical analysis must be made and documented before locking the database. Data will be retained for at least 15 years after investigation closure.

XII. DEVIATIONS FROM THE CLINICAL INVESTIGATION PLAN

a) *Definition of deviation (ISO 14155: 2020)*

Instance of failure to follow, intentionally or unintentionally, the requirements of the CIP

A study deviation is an event where the investigator or investigation site personnel did not conduct the clinical study according to the Clinical Investigation Plan or Clinical Investigation Agreement.
The investigator is not allowed to deviate from the above-mentioned documents except with prior approval. All deviations shall be documented and explained, regardless the reason for the deviation.
Examples of protocol deviations include but are not limited to the following:

- Failure to obtain informed consent (either signed patient Informed Consent) prior to participation
- Incorrect version of the Patient Informed Consent used
- Failure to obtain EC approval before the start of the study
- Implanted subject did not meet inclusion/exclusion criteria
- Follow-up visit not done
- Adverse events not reported in the required time frame as required by regulation or as specified in the CIP
- Source data permanently lost
- Enrollment of patients during lapse of EC approval

b) *Request for approval of study deviations*

The investigator shall obtain documented approval from Symbios, before implementation, for any change in or deviation from the Clinical Investigation Plan. In case of study deviations that can affect the subject's rights, safety and well-being or the scientific integrity of the clinical study, approval from the local EC must also be obtained before implementation. The investigator shall timely contact the Clinical Affairs Manager for review of the proposed change/deviation.
Prior approval is not always realistic in situations where unforeseen circumstances are beyond the investigator's control. However, also in these cases, the event is considered a deviation, and shall be reported.
In any emergency situation the investigator shall exercise his judgment to safeguard the subject's interest. Such deviations from the Clinical Investigation Plan do not require the prior approval of Symbios. The investigator shall report the deviation as soon as possible to Symbios and the applicable local EC.

c) *Reporting requirements for study deviations*

Study deviations should be reported to Symbios via the Study Deviation e-CRF excel table. Relevant information for each deviation will be documented by site personnel and reviewed by the Investigator.
Investigators should report the following deviations to Symbios and their reviewing EC:

- Failure to obtain written informed consent
- Deviations to protect the life or physical well-being of a subject in an emergency

In addition, Investigators are required to adhere to local EC procedures for reporting deviations.
Symbios is responsible for analyzing deviations, assessing their significance, and identifying any corrective and/or preventive actions that may be necessary. Repetitive or serious investigator compliance issues may represent a need to initiate a corrective action plan, which may include suspension of enrollment or termination of the investigator's or site's participation in the study. The deviations will be traced periodically and followed-up by monitor together with the study personal and the PI.

XIII. STATEMENT OF COMPLIANCE

This clinical study will be conducted in compliance with the latest version of the Declaration of Helsinki (2013), the international standard ISO 14155, laws and regulations of the countries in which the clinical study is conducted, including data protection laws, the Clinical Investigation Agreement and the Clinical Investigation Plan. At the EU level, the study will also be compliant with Regulation (EU) 2016/679 (General Data Protection Regulation), and a new EU Regulation on medical devices (MDR 2017/754), which has entered into force on May 25, 2017, with a transition period. The MDR will fully apply in EU Member States from May 26, 2021 and will replace the existing directives and will apply for this study for reporting of serious adverse events and device deficiencies.

Symbios and participating investigators will conduct the clinical investigation in accordance with the ethical principles described above and will be compliant with International Conference and Iguidance and any regional or national regulations, as appropriate.

The clinical investigation (CIP & PIC) shall begin upon local EC approval; as written approval from competent authority is not required (PMCF study). Approval of both the protocol and the consent form must be obtained before any participant is enrolled. Other documents that are referred to this Clinical Investigation Plan in the APPENDICES and are listed below, will be made available upon request: • Instructions for Use • Case Report Forms • Monitoring Plan • Data Management Plan • Statistical Analysis Plan

Any amendment to the protocol will require review and approval by the EC before the changes are implemented to the study. If the EC imposes any additional requirements (e.g. safety reports, progress reports etc.), Symbios will prepare the required documents and send them to the investigator for reporting to the EC. Investigators must inform Symbios of any change in status of EC approval once the investigation site has started enrolment. If any action is taken by an EC with respect to the investigation, that information will be forwarded to Symbios by the respective investigator.

Pediatric, legally incompetent, or otherwise vulnerable patients are not eligible for the study.

Symbios will maintain appropriate clinical study liability insurance coverage if required under German applicable laws and regulations and will comply with applicable law and custom concerning specific insurance coverage.

A clinical study agreement between sponsor, institution and the Principal Investigator will be executed prior to any clinical activities.

XIV. AMENDMENTS TO THE CIP

The CIP, CRFs, informed consent form, or other clinical investigation documents such as instructions for use shall be amended as needed throughout the clinical investigation in accordance with written procedures for the control of documents and document changes.
Documentation of changes shall include a description of the changes, justification of the changes and their potential impact on the performance, effectiveness, safety or other endpoints, and identification of the affected documents.

The investigator could propose any appropriate modification(s) of the Clinical Investigation Plan or product use. Symbios will review this proposal and decide whether the modification(s) will be implemented to the CIP. Symbios will submit any significant amendment to the Clinical Investigation Plan, including a justification for this amendment, to the appropriate EC and to the Principal investigator. The version number and date of amendments shall be documented. The PI will only implement the amendment after approval of the EC, and sponsor. Furthermore, co-investigators shall sign any approved amendment for agreement.

If the amendment impacts the integrity of the clinical investigation, the data collected before and after the amendment shall be analyzed statistically to assess the effect of the amendment on performance, effectiveness or safety analysis. This analysis shall be included in the clinical investigation report.

XV. PATIENT INFORMATION PROCESS

The Patient Information Consent form will consist of an information form and a signature form. Subject selection will be based on the defined inclusion/exclusion criteria. Each patient who meets the inclusion criteria will be informed about this study before any data is collected. This information will be given during the preoperative consultation, during which the surgeon will give to the patient the information letter & the signature form (See. Chapter XXI. APPENDICES. D. PATIENT INFORMATION SHEET), and will be available to answer any questions.

This information letter will contain information regarding study design and investigational devices. It will explain risks/benefits for patients willing to participate in the study. It will also give information on the planned schedule of assessment, and follow-up visits up to 2 years. Subjects willing to participate will then sign the consent form, which will be the start of the enrolment process, prior to randomization process for ARM 1: ORIGIN PS or ARM 2: VANGUARD PS.

At any time and during the course of the study, each subject has a real freedom of choice to participate in this study. If he/she agrees, he/she has the right to access and rectify his/her data but also the right to withdraw his/her consent when he/she wishes, as simply as he/she has decided to grant it. This includes the right to erase the collected data and the right to object to the use of such data.

The process of how the Patient Informed Consent form has been obtained, will be described in the patient's medical file.

XVI. ADVERSE EVENTS, ADVERSE DEVICE EFFECTS AND DEVICE DEFICIENCIES

For the purpose of this study, Symbios will classify each category of adverse events based to the ISO 14155: 2020.

A. Adverse event

Untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects, users or other persons, whether or not related to the investigational medical device and whether anticipated or unanticipated
Note 1: This definition includes events related to the investigational medical device or the comparator.
Note 2: This definition includes events related to the procedures involved.
Note 3: For users or other persons, this definition is restricted to events related to the use of investigational medical devices or comparators.

B. Adverse Device Effect

Adverse event related to the use of an investigational medical device
Note 1: This definition includes adverse events resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation, or any malfunction of the investigational medical device.
Note 2: This definition includes any event resulting from use error or from intentional misuse of the investigational medical device.
Note 3: This includes 'comparator' if the comparator is a medical device.

C. Serious adverse events

Adverse event that led to any of the following:
a) death,
b) serious deterioration in the health of the subject, users, or other persons as defined by one or more of the following:

1. a life-threatening illness or injury, or
2. a permanent impairment of a body structure or a body function including chronic diseases, or
3. in-patient or prolonged hospitalization, or
4. medical or surgical intervention to prevent life-threatening illness or injury, or permanent impairment to a body structure or a body function,

c) foetal distress, foetal death, a congenital abnormality, or birth defect including physical or mental impairment
Note 1: Planned hospitalization for a pre-existing condition, or a procedure required by the CIP, without serious deterioration in health, is not considered a serious adverse event.

D. Serious health threat

Signal from any adverse event or device deficiency that indicates an imminent risk of death or a serious deterioration in the health in subjects, users or other persons, and that requires prompt remedial action for other subjects, users or other persons
Note 1: This would include events that are of significant and unexpected nature such that they become alarming as a potential serious health hazard or possibility of multiple deaths occurring at short intervals.

E. Serious adverse device effect

Serious adverse device effect which by its nature, incidence, severity or outcome has not been identified in the current risk assessment
Note 1: Anticipated serious adverse device effect (ASADE) is an effect which by its nature, incidence, severity or outcome has been identified in the risk assessment.

F. Unanticipated Serious Adverse Device Effect

Serious adverse device effect which by its nature, incidence, severity or outcome has not been identified in the current risk assessment
Note 1: Anticipated serious adverse device effect (ASADE) is an effect which by its nature, incidence, severity or outcome has been identified in the risk assessment.

G. Device Deficiency

Inadequacy of a medical device with respect to its identity, quality, durability, reliability, usability, safety or performance
Note 1: Device deficiencies include malfunctions, use errors, and inadequacy in the information supplied by the manufacturer including labelling.
Note 2: This definition includes device deficiencies related to the investigational medical device or the comparator.

H. Regulatory requirements for reporting

An Unanticipated Adverse Device Effect (UADE) is defined as any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan, or any other unanticipated serious events associated with the ORIGIN System that relates to the rights, safety, or well-being of patients. All unanticipated adverse device effects must be reported to the Sponsor no later than 24 hours after it occurs.

The following list of safety outcomes should be collected in the eCRF case report form which will trigger a notification to Symbios regulatory department via regulatory@symbios.ch:

- Serious Adverse Events (SAEs)
- Unanticipated Adverse Device Effects (UADEs)
- Devices deficiencies
- Non-serious Adverse Events related to the device or study procedure
- Secondary surgical procedures or revisions
- Surgical complications

All above-mentioned Adverse events will be reported in the final report of the Clinical Investigation.

In accordance with the European Medical Device Directive (MDR), ISO 14155 and with MEDDEV 2.12/1, any serious adverse event, related to the device under evaluation, will be announced by the manufacture:

- To its Notified Body and
- To the relevant competent authority in Germany.

XVII. EARLY TERMINATION OR SUSPENSION OF THE STUDY

A. Early study suspension or termination

Symbios or Regulatory Authority may decide to suspend or prematurely terminate the clinical study. If the clinical study is terminated prematurely or suspended, Symbios shall inform the investigators and regulatory authorities (applicable local EC in Germany) of the termination or suspension and the reason(s) for this. The investigator shall then inform the study subjects.

B. Early investigation site suspension or termination

The early termination could happen in two cases:

- Symbios, EC or Regulatory Authority may decide to suspend or prematurely terminate an investigation site. Symbios shall inform the investigator of the termination or suspension and the reason(s) for this. The investigator shall then inform the study subjects.
- When the risks are found to outweigh the potential benefits, investigators must assess whether to continue, modify or immediately stop the clinical study in the respective investigation site and immediately inform the sponsor and EC, if applicable.

C. Subject follow-up in case of termination

In case of early termination, all subjects should be followed by their physicians per their standard hospital practice and no further patient data will be collected under this Clinical Investigation Plan.

D. Study close out

A study close-out visit will be performed on site with Symbios or its representative. Study close-out visits will be performed to ensure that study data are correctly entered on the e-CRFs and all patients are exited from the study. In addition, all open queries should be resolved and closed. During this visit, the monitor will also ensure that the Investigator Site File is up to date and complete and that any outstanding action items from previous visits have been resolved.

After study close-out, all patients will be followed accordingly to the hospital's standard of care practices.

Symbios and/or its designees will notify the site in writing of the intention to close the study and if required will notify/report to applicable local EC.

XVIII. DATA STORAGE AND PROTECTION

a) *Data Integrity & Confidentiality*

All information and data sent to parties involved in study conduct concerning patients or their participation in this study will be considered confidential. Each enrolled subject will be assigned a unique study ID number, which is pre-configured in the Symbios eCRF.

Records of the subject/study ID number relationship will be maintained by the site, in the patient's file and on the subject identification log. The study ID number is to be recorded on all study documents to link them to the subject's medical records at the site. To maintain confidentiality, the subjects' name or any other personal identifiers will not be recorded on any study document other than the Patient Informed Consent. In the event a subject's name is included for any reason, it will be blinded as applicable. In the event of inability to blind the identification (e.g., digital media), it will be handled in a confidential manner by the authorized personnel, listed on the Delegation Task List (DTL), which will be stored in the Investigator Site File. Study personnel delegated for e-CRF completion will be trained on the use of the EDC system and thereafter provided with a username and password to access the system. The e-CRFs must be completed and/or updated to reflect the latest observations on the subjects participating in the study. The investigator (or approved sub-investigator) will electronically sign the appropriate pages of each e-CRF.

Confidentiality of data will be observed by all parties involved at all times throughout the clinical investigation. All data shall be secured against unauthorized access. The privacy of each subject and confidentiality of his/her information will be preserved in reports and when publishing any data.

b) *Data protection (GDPR[9] or General Data Protection Regulation)*

Entered data in CRF must be traceable to source documents on site. Source documentation is defined as the first time the data appear and may include all clinical records, hospital records, procedural reports, autopsy reports, and any other material that contains original information used for study data collection or adverse event reporting. Where copies of the original source document as well as print outs of original electronic source documents are retained (for AEs recording), these shall be signed and dated by a member of the investigation site team with a statement that it is a true reproduction of the original source document.

The Investigator must ensure the availability of source documents from which the information on the e-CRFs was derived. In addition, the medical records of study subjects should be marked or flagged in such a way to indicate their participation in the study. All data used in analysis and reports will be used without identifiable reference to the subject. All data will be secured against unauthorized access. Each original form will be kept by the investigator during 15 years.

[9] https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32016R0679

XIX. PUBLICATION

Symbios will remain principal owner of the study data. Therefore, collected data cannot be distributed to a third party without authorization of the sponsor. Submission of all abstracts and publications regarding the primary endpoint and secondary endpoints from the study requires approval by the Principal Investigators (designated advisory committee) and by the designed responsible at Symbios. Additional information is displayed in the Clinical Study Agreement and is applicable to this protocol.

XX. BIBLIOGRAPHY

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K. Giesinger y, D.F. Hamilton z, B. Jost y, B. Holzner x, J.M. Giesinger

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Simon M. Thompson, MBBS, MD(Res), FRCS(Tr & Orth), Lucy J. Salmon, BappSci(Physio), PhD,

Justin M.Webb, MBBS, FRACS, Leo A. Pinczewski, MBBS, FRACS, Justin P. Roe, MBBS, FRACS

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DOI 10.1186/s12891-016-1001-3

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Benjamin Wheatleya,⁎, Kyle Nappoa, Jesse Fischb, Laura Regob, Molly Shayb, Christopher Cannovab

Received 28 October 2018; Accepted 26 November 2018

0972-978X/ Published by Elsevier, a division of RELX India, Pvt. Ltd on behalf of Prof. PK Surendran Memorial Education Foundation.

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Emmanuel Thienpont, MD, MBA a, Gaetan Opsomer, MD a, Angelique Koninckx, MD a, Frederic Houssiau, MD, PhD

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C. A. Kahlenberg,, S. Lyman,, A. D. Joseph,, Y-F. Chiu, D. E. Padgett

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Simon W. Young FRACS, Matthew L. Walker FRACS, Ali Bayan FRACS, Toby Briant-Evans FRCS, Paul Pavlou FRCS, Bill Farrington FRCS, FRACS

Published online: 25 April 2016

DOI 10.1007/s11999-016-4844-x

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Validation of a New Patient-Reported Outcome Measure

Henrik Behrend, MD,* Karlmeinrad Giesinger, MD, MSc,* Johannes M. Giesinger, MSc, PhD,y and Markus S. Kuster, MD, PhD*

Submitted August 9, 2010; accepted June 15, 2011.

doi:10.1016/j.arth.2011.06.035.

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D. F. Hamilton, F. L. Loth, J. M. Giesinger, K. Giesinger, D. J. MacDonald, J. T. Patton, A. H. R. W. Simpson, C. R. Howie

Received 22 June 2016; Accepted after revision 13 October 2016

doi:10.1302/0301-620X.99B2.BJJ-2016-0606.R1 $2.00

XXI. APPENDICES

A. ABBREVIATIONS

Abbreviation	Term
AE	Adverse Event
ADE	Adverse Device Effect
AP	Antero Posterior
CER	Clinical Evaluation Report
CIM	Customized Individually Made
CIP	Clinical Investigation Plan
CRO	Contract Research Organization
e-CRF	Electronic Case Report Form
EDC	Electronic Data Capture
EC	Ethical Committee
FJS	Forgotten Joint Score
GCP	Good Clinical Practices
GDPR	General Data Protection Regulation
HKA	Hip-Knee-Ankle
HKS	Hip-Knee-Shaft
ICF	Informed Consent Form
ISF	Investigational Site File
IFU	Instructions for use
KOOS	Knee Injury and Osteoarthritis Outcome Score
KSRESS	Knee Society Radiographic Evaluation and Scoring System
KSS	Knee Society Score
MCID	Minimal Clinical Important Difference
OKS	Oxford Knee Score
OTS	Off-The-Shelf
PI	Principal Investigator
PIS	Patient Information Sheet
PMCF	Post-Market Clinical Follow-up
PMS	Post-Market Surveillance
PRO	Patient reported outcome
PROMs	Patient reported outcome measures
SAE	Serious Adverse Event
SADE	Serious Adverse Device Effect
SAP	Statistical Analysis Plan
SD	Source Document
SLS	Single Leg Stance

SOP	Standard Operating Procedures
TKA	Total Knee Replacement Arthroplasty
TUG	Timed Up and Go
U(S)ADE	Unanticipated (Serious) Adverse Device Effect

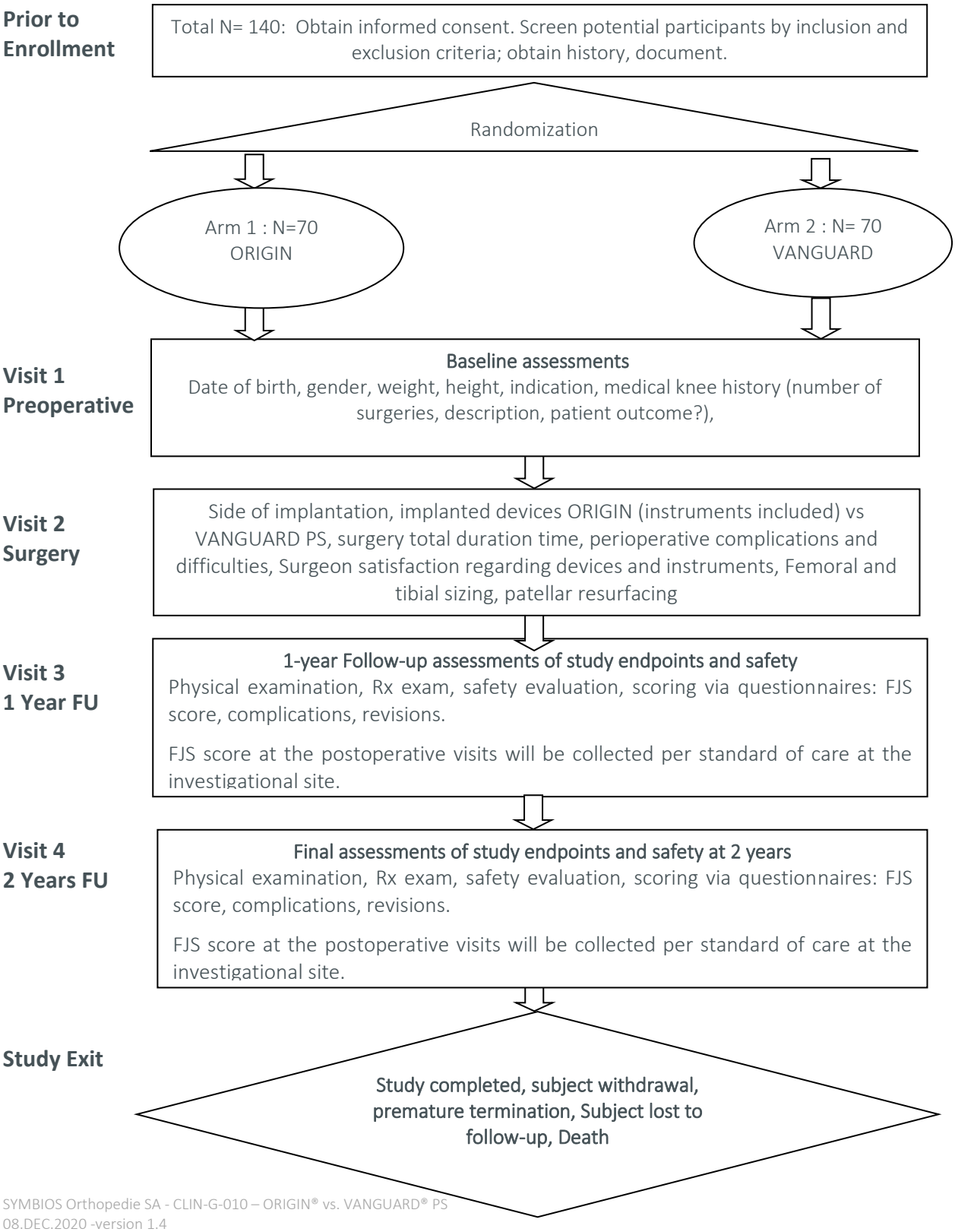
B. SCHEDULE OF ASSESSMENT

Patient visits/Activities	1 Preoperative	2 OP	3 12 Months[10] (1 Year)	4 24 Months (2 Years)[11]
Patient Informed Consent	X			
Demographic data	X			
Indications	X			
Medical History	X			
Clinical examination	X		X	X
Randomization: allocation to two study arms: *CT-Scan (KNEE PLAN) - ARM 1: ORIGIN Group*	X			
Preoperative Radiological assessment for ARM 1& ARM 2	X			
Surgery		X		
Clinical Examination at 1 y and 2 y follow-up			X	X
Radiological Assessment at 1y and 2 y FU			X	X
Knee Injury and Osteoarthritis Outcome Score (KOOS)	X		X	X
Oxford Knee Score (OKS)	X		X	X
Quality of life (EQ-5D-5L)	X		X	X
Forgotten Joint Score (FJS)	X		X	X
Patient satisfaction questionnaire	X		X	X
Complications & Revisions		X	X	X

[10] The follow-up window is flexible and is set as a guidance to +/-1M for the first visit.

[11] For FU visits at 2 years, it is assumed that the visits will be planned per standard of care. (window set at +/- 2 month)

C. RANDOMIZATION FLOW CHART



D. KNEE INSTRUMENTS TO EVALUATE

symbios custom-made for you	KNEE INSTRUMENTS KNEE-PLAN Guides/KNEE PLAN Set/Add-ON Instrumentation
SURGICAL STEPS	INSTRUMENTS TO USE
DISTAL FEMORAL CUT	ORIGIN® KNEE-PLAN® Femoral Cut Guide Drill Pin -Ø3.2 mm x 70 mm -9000 0031 Drill Pin Adapter -9000 0019 Resection Controller -9000 0003 EM Alignment Rod -9000 0008 Pin Removal Forceps -9000 0010 KNEE-PLAN® Femoral Bone Model
A/P FEMORAL CUTS AND CHAMFER CUTS	Drill Pin - Ø3.2 mm x 70 mm -9000 0031 Drill Pin Adapter -9000 0019 ORIGIN® 4-in-1 Femoral Cuts Guide -9000 781x Resection Controller 9000 0003 Pin Removal Forceps - 9000 0010
INTERCONDYLAR CUTS	ORIGIN® PS Intercondylar Cuts Guide -9000 7703 Drill Pin - Ø3.2 mm x 70 mm -9000 0031 Drill Pin Adapter -9000 0019 Stop Drill Bit -Ø6 mm x 24 mm -9000 4003 Pin Removal Forceps -9000 0010
FEMUR TRIAL-EVALUATION OF THE DEFORMATION	ORIGIN® PS Trial Femur -9000 7701
PROXIMAL TIBIAL PRE CUT	ORIGIN® KNEE-PLAN® Tibial Cut Guide 9002 1209 KNEE-PLAN® Tibial Bone Model -9002 1092 Drill Pin - Ø3.2 mm x 70 mm -9000 0031 Drill Pin Adapter -9000 0019 Pin Removal Forceps- 9000 0010 KNEE-PLAN® Tibial Bone Model
PRE-TRIALS AND TIBIAL CUT ADJUSTMENT	Single-Use Impaction/Extraction Handle -9000 7600/9000 7610 Single-Use Femoral Impaction Head -9000 7602/9000 7612 ORIGIN® PS Trial Femur-9000 7701 ORIGIN® PS Fixed Trial Insert +2 mm -9000 7712 Single-Use Recut Guide -9000 7030/9000 7031

symbios custom-made for you	KNEE INSTRUMENTS KNEE-PLAN Guides/KNEE PLAN Set/Add-ON Instrumentation
SURGICAL STEPS	INSTRUMENTS TO USE
TIBIAL BASE PLATE PREPARATION	ORIGIN® PS Tibial Drill Guide Ø15 mm -9000 7704 Drill Pin - Ø3.2 mm x 70 mm -9000 0031 Drill Pin Adapter -9000 0019 Stop Drill Bit - Ø15 mm x 69 mm -9000 4005 Pin Removal Forceps -9000 0010 ORIGIN PS Tibial Drill Guide Adaptor- 9000771X Stop Drill Pin– Ø11mm x 124mm - 9000 4004 ORIGIN Single-Use Tibial Keel Broach – 9000 78XX
FINAL TRIALS	ORIGIN® PS Fixed Trial Tibia -9000 7702 Single-Use Impaction/Extraction Handle -9000 7600/9000 7610 Single-Use Tibial Impaction Head -9000 7601/9000 7611 Single-Use Tibial Insert Impaction/Extraction Head 9000 7604/9000 7613 ORIGIN® PS Fixed Trial Insert +0 mm -9000 7710 ORIGIN® PS Fixed Trial Insert +2 mm -9000 7712 Single-Use Impaction/Extraction Handle -9000 7600/9000 7610 Single-Use Femoral Impaction Head -9000 7602/9000 7612 ORIGIN® PS Trial Femur-9000 7701 Single-Use Impaction/Extraction Handle-9000 7600/900 7612 Single-Use Tibial Insert Impaction/Extraction Head -9000 7604/9000 7613 ORIGIN® PS Trial Tibia Modular-9000 77XX
PATELLAR PREPARATION *(if applicable)*	Patella Cutting Clamp -9400 0001 Drill Pin -Ø3.2 mm x 70 mm -9000 0031 ORIGIN® Patella Trial Component M -9000 7803 Drill Pin -Ø3.2 mm x 70 mm-9000 0031 ORIGIN® Patella Drill Tip M -9400 2003 Patella Compression Clamp -9400 0002 Stop Drill Bit -Ø6 mm x 24 mm -9000 4003

symbios custom-made for you	KNEE INSTRUMENTS KNEE-PLAN Guides/KNEE PLAN Set/Add-ON Instrumentation
SURGICAL STEPS	INSTRUMENTS TO USE
IMPLANTATION	Single-Use Impaction/Extraction Handle -9000 7600/9000 7610 Single-Use Tibial Impaction Head -9000 7601/9000 7611 Single-Use Tibial Insert Impaction/Extraction Head 9000 7604/9000 7613 Single-Use Femoral Impaction Head -9000 7602/9000 7612 Patella Compression Clamp -9400 0002 Patella Compression Tip -PD000 069

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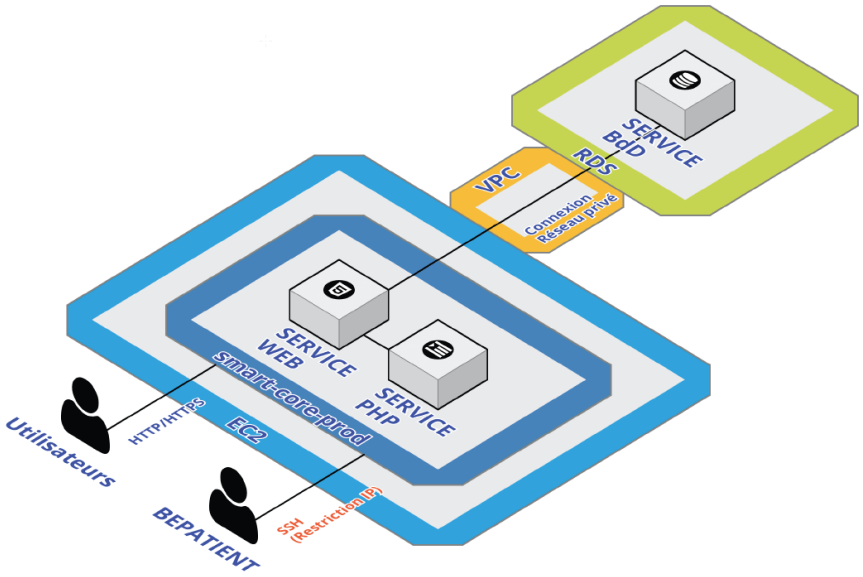
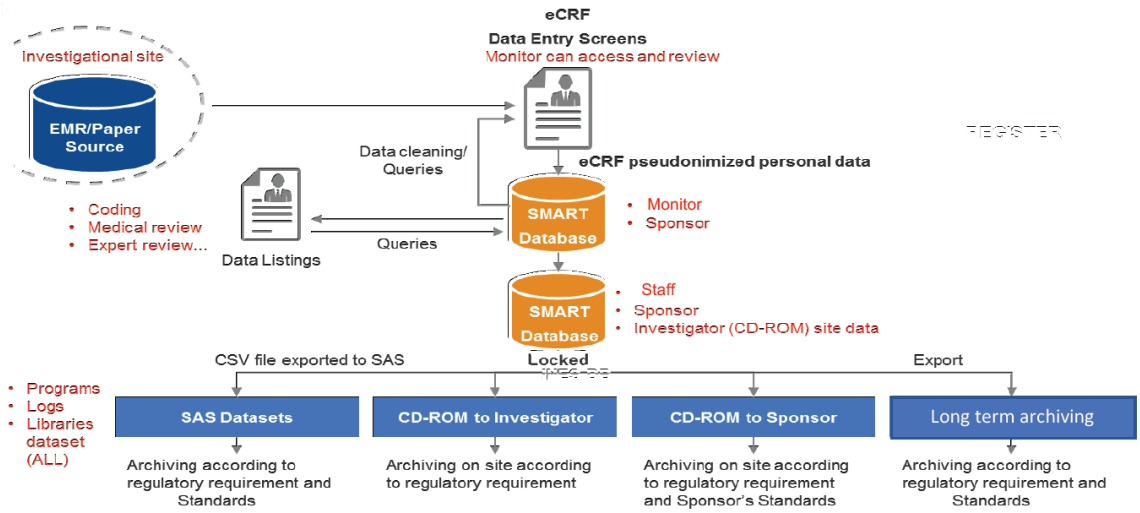
Doug A. Dennis, M.D. e, Giles R. Scuderi, M.D. f
http://dx.doi.org/10.1016/j.arth.2015.05.049

F. BEPATIENT DATA HANDLING



Scheme of the data treatment by Symbios.

General scheme of the data treatment by Bepatient
Scheme of the data treatment by Symbios.
(All data export possibilities are given as an indication)



Please provide a brief description of your IT infrastructure
All our servers are based on cloud service. The servers are using EC2 Service, and the database is provided by RDS service. The servers can only be connected in SSH using our bastion.

Description of your data centers
Amazon AWS is BePATIENT sub-contractor for data hosting. Data are hosted in Europe.

Description of your hosting services
3 different environments (DEV - BETATESTING - LIVE)
Monitor
StaffLong term

Description of your back-up process (type, frequency)
The backup of our EDC system is made on a daily routine. We are saving all the website folders into AWS S3 encrypted bucket. The backup of the DB is made by a snapshot built-in AWS RDS service. Application Backup >
DEV Server: Every morning at 5:00 am (GMT + 1)
BETA Server: Every morning at 6:00 am (GMT + 1)
LIVE Server: Every morning at 4:00 am (GMT +1 time)
Database Backup >
Snapshots of the database is made every nights at 2:00 am (GMT + 1)

Please describe your disaster recovery and business continuity processes
Contingency plan corresponds to implemented processes to guarantee service continuity and alternative solutions in case of material or digital incident.
In case of material issues, information are contained on AWS documentation, (system availability: 24/24, 7/7 and support: 24h maximum and as soon as possible).
In case of applicative issues, BePATIENT guarantees support Monday to Friday included
9:00am to 6:00pm (UTC/GMT +10h).

About business continuity, each commercial relation with our clients are described in a contract document. The business continuity plan is described in a contract section which is specific to each client. In case of buyout business, the new owner is the only one who can decide if BePATIENT contracts are maintained or not but in any case, BePATIENT must notify clients at least 2 months before business change.

A. INSTRUCTION FOR USE (separate document)

B. PATIENT INFORMATION SHEET (separate document)

C. CASE REPORT FORMS (separate document)

D. ADVERSE EVENTS FORM (separate document)

E. MONITORING PLAN (separate document)