



Postoperative Outcomes Within Enhanced Recovery After Surgery Protocol in Elective Total Hip and Knee Arthroplasty. POWER.2 Study: Study Protocol for a Prospective, Multicentre, Observational Cohort Study

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Abstract

Objective: The number of indications for total hip replacement (THR) and total knee replacement (TKR) surgery is increasing. Enhanced recovery after surgery (ERAS) represents the next step in the evolution of standardised care. The primary aim of this study is to measure the in-hospital 30-day medical and surgical postoperative complications rate. The study's secondary aims are to determine the length of stay, 30-day mortality rate, 30-day reoperation and readmission rates, the ERAS overall compliance and predefined ERAS individual items compliance.

Methods: This multicentre, prospective, observational study will include adult patients (aged >18 years) undergoing elective THR and TKR surgery. Consecutive patients undergoing surgery within the 2-month data collection period will be included. Centres that offer the THR and/or TKR surgery will be eligible to participate. The data collection will be done through an online data collection form via a secure, password-protected platform at each centre with predefined data fields.

Results: Ethical approval for this study has been obtained from the Comité de Ética de la Investigación de la Comunidad Autónoma de Aragón (C.P.-C.I. PI18/135; on 23 May 2018). It was prospectively registered on 27 June 2018, at www.clinicaltrials.gov with identification no. NCT03570944.

Conclusion: The study will be disseminated through the SPARN-RedGERM, SEDAR, GERM and through social media. Peer-reviewed publications will be published under corporate authorship, including POWER.2 Study Group and SPARN-RedGERM.

Keywords: Arthroplasty, arthroplasty, follow-up studies, hip, knee, outcome and process assessment (health care), replacement

Introduction

Joint replacement surgery for both the hip and knee is one of the most common elective surgical procedures carried out in Europe and in the United States (1). The number of indications for total hip replacement (THR) and total knee replacement (TKR) surgery is increasing, and a considerable growth in the number of THR and TKR surgical procedures is foreseen during the next decade, which make these surgeries one of the most expensive processes for health services (2). It is increasingly evident that a sustainable model for joint replacement surgery should emphasise value without compromising patient outcomes. Early functional recovery and hospital stay are important for surgeons, patients and health administrators.

THR and TKR are associated with a low risk of morbidity and mortality compared to other surgeries. In general, mortality rates after THR and TKR are approximately 0.2%, with morbidity rates of approximately 2.9% (2). Enhanced recovery after surgery (ERAS) involves the use of multiple perioperative strategies to facilitate the best conditions for surgery and recovery, in an effort to achieve faster hospital discharge and a rapid resumption of normal activities after surgery, through the reduction of perioperative stress. Although individual components may vary, most ERAS programmes include avoiding prolonged fasting, preoperative optimisation of health (recommendations on diet, alcohol consumption, etc.), preoperative carbohydrate loading, patient blood management, goal-directed haemodynamic therapy, multimodal analgesia with opioid avoidance, early withdrawal of tubes (drains, urinary catheter), support of the gastrointestinal function and mobilisation and early feeding (3).

The ERAS protocols have shown repeatedly that they reduce the length of hospital stay (4, 5) without influencing the rates

of complications or readmission in abdominal surgery (4, 5). Despite widespread success in multiple surgical subspecialties, ERAS remains poorly studied and poorly reported in orthopaedic surgery literature. Berend et al. (6) found that adopting a holistic programme of perioperative enhanced recovery reduced inpatient stays and readmissions after THRs and TKRs. However, the authors only reviewed the non-surgical measures and concluded that they can be effective in accelerating recovery. They suggested combining these measures with minimally invasive surgery to achieve the best possible results and a faster recovery (6).

Our objective is to carry out a 60-day state cohort study of patients older than 18 years undergoing elective THRs and TKRs with or without an ERAS programme with any level of compliance with an ERAS protocol (0%-100%) to provide detailed data describing postoperative complications, associated mortality and hospital stay and in addition, to determine if the application of an ERAS programme affects postoperative complications in patients undergoing elective THRs and TKRs and which ERAS individual components have an impact on clinical outcomes.

Methods

Study objectives

The primary aim of POWER.2 is to determine the incidence of predefined medical and surgical postoperative complications at 30 days of follow-up after elective THRs and TKRs in centres with or without an ERAS protocol with any level of protocol compliance (from 0% to 100%). The secondary aims of this study are to determine in-hospital mortality, assess the relationship between ERAS compliance and postoperative complications and assess the influence of each of the predefined ERAS items on postoperative complications.

Study design

We aim to undertake a prospective, multicentre, observational cohort study of consecutive patients undergoing elective THRs and TKRs.

Setting

This study will take place across anaesthesiology and orthopaedic surgery units across Spain over a consecutive period of 2 months. Any hospital that offers THRs and/or TKRs will be eligible to participate.

Recruitment

All patients undergoing an elective THRs and TKRs in Spanish participating centres will be eligible for the study. Since adherence to the ERAS protocol will be assessed, no potential hospital will be excluded for having or not having an established ERAS protocol, or for the adherence to ERAS.

Eligibility Criteria

Inclusion criteria

All adult patients (aged >18 years) undergoing an elective THR and TKR surgical procedure will be eligible for this study. Types of approaches for TKRs will include medial parapatellar, midvasto and subvasto (others), with surgical technique of both components cemented, hybrid (not cemented femoral and cemented tibial) or not cemented.

Types of approaches for THRs include posterolateral, anterolateral, lateral direct and direct anterior (other), with surgical technique of both components cemented, hybrid (femoral cemented and acetabular not cemented) or not cemented.

Exclusion criteria

Patient refusal, patients undergoing emergency surgery; patients undergoing partial prostheses, prostheses revision or replacement surgeries will be excluded from the study.

Outcome measures

The primary outcome measure is in-hospital 30-day postoperative complications.

Complications are defined and graded according to the standards for definitions and use of outcomes for clinical effectiveness research in perioperative medicine: European Perioperative Clinical Outcome definitions (7), the standardised list and definitions of the Knee Society (8), the Standardised List, Definitions and the Stratification Developed by the Hip Society (9); and the definition and severity of bleeding results from an adaptation from the standardised bleeding definitions for cardiovascular clinical trials (Supplementary Material, Tables 1-3) (10).

Secondary outcome measures will include the length of stay, 30-day mortality rates, 30-day reoperative and readmission rates, the ERAS overall compliance and ERAS individual items compliance. The level of care after surgery will also be recorded as defined in Table 1. Patient timeline is described in Figure 1.

Data Collection and Data Management

Each participating local hospital will be responsible for identifying potentially eligible patients for study recruitment. The principal investigator team will consist at least, but not limited to, a consultant orthopaedic surgeon and/or a consultant anaesthetist. Patients will be identified from three clinical areas-outpatient clinic, preoperative assessment clinic and daily elective operating lists-to ensure all potentially eligible patients are captured.

The data collection will be done through an online data collection form via a secure, password-protected platform at each centre with predefined data fields. All data will be anonymised, so patients cannot be tracked, and all anonymised

TIMEPOINT	STUDY PERIOD							
	Enrolment	Day of surgery	Follow-up					Close-out
	-t ₁	0	Day 1	Day 2	Day 3	Day 4	etc.	30 day
ENROLMENT:								
Eligibility screen	X	X						
Informed consent	X	X						
Inclusion		X						
FOLLOW-UP			←-----→					
ASSESSMENTS:								
Preoperative Variables	X							
Intraoperative variables		X						
Postoperative variables and clinical outcomes			X	X	X	X	X	X

Figure 1. Schedule of enrolment, interventions and assessments

Table 1. Level of care after surgery
1. Critical care Level 3: Includes advanced organ support, for example, invasive ventilation and renal replacement therapy.
2. Critical care Level 2: May include advanced cardiorespiratory monitoring (e.g. invasive arterial/central venous monitoring) and basic organ support (e.g. non-invasive ventilation and inotropic/vasoactive drug administration).
3. Post-anaesthetic care unit: Care within a designated area for the patients in the immediate recovery from anaesthesia. May deliver care at Levels 1 to 3.
4. Surgical ward (Level 0/1): Normal ward care without Level 2 or 3 capabilities.
The level of care should be defined according to the care the patient received rather than the location. For example, a patient receiving Level 2 care in a Level 3 area should be recorded as receiving Level 2 care.

Table 2. ERAS compliance definitions (adapted from 3)

	ERAS Included Individual Items	Definitions of ERAS Compliance for Included Individual Items
1	Presurgical education	Received verbal and written ERAS education at a dedicated preadmission visit
2	Presurgical optimisation	Patients stopped smoking 4 weeks before surgery, and alcoholics ceased all alcohol consumption 4 weeks before surgery
3	Preoperative fasting	Preoperative fasting limited to 2 hours for clear liquids (water, coffee, juice without pulp), and at 6 hours for solids
4	Patient blood management	Set of measures applied to optimise preoperative haemoglobin, avoid bleeding and avoid transfusion
5	Preoperative carbohydrate drinks preload	Given preoperative carbohydrate drink. Defined as at least 50 g carbohydrate in at least 400 mL fluid in the form of a dedicated preoperative beverage with a proven safety profile. Given up until 2 hours before anaesthesia
6	Avoidance of long-acting sedative premedication	No long-acting sedative premedication given (e.g. opioids, sedative antihistamines and neuroleptics)
7	Thromboprophylaxis	Given thromboprophylaxis; low-molecular-weight heparin and compression stockings
8	Antibiotic prophylaxis	Given antibiotic prophylaxis before skin incision
9	Regional anaesthesia	Anaesthetic procedure that allows rapid awakening, adequate analgesia and patient recovery. The item is considered positive provided that any major anaesthetic technique (spinal anaesthesia or general anaesthesia) is accompanied by local or locoregional anaesthesia techniques; or continuous epidural anaesthesia
10	PONV prophylaxis	Given PONV prophylaxis
11	Active prevention of unintentional hypothermia	Use of fluid heaters and/or thermal blanket for all patients during the surgical procedure
12	Goal-directed fluid therapy	Intravenous fluid administration guided by haemodynamic goals based on the cardiac output or derived monitoring by any validated cardiac output monitoring
13	Postoperative analgesia	A multimodal analgesic management that includes at least two drugs in order to avoid or reduce the administration of morphics
14	Postoperative glycaemic control	Patients receive glycaemic control in the first 24 hours, for target glycaemia <180 g dL ⁻¹
15	Early mobilisation	Defined as the patient move at least to armchair in the first 12 postoperative hours
16	Early feeding	Defined as the patient tolerates oral feeding in the first six postoperative hours

ERAS: enhanced recovery after surgery; PONV: postoperative nausea and vomiting

data will be submitted centrally. A list of patients will be used in each centre to match identification codes in the database of individual patients to record the clinical results and provide any data that may be missing. The required anonymous data fields of this data collection form are shown in Tables 2-5 and include demographic, surgery and anaesthesia related variables, Patient Blood Management variables and ERAS individual item compliance. All anonymised data will be subsequently analysed. Outcome data specific to each surgeon or centre who participates in the study will not be analysed.

Statistical analysis

Sample size calculation

Our plan is to recruit as many centres as possible on a national basis and ask them to include all eligible patients in

the study. Only those centres that include at least 10 valid patients will be included in the final data analysis. Those centres that present a smaller number of patients recruited will be evaluated individually, according to their characteristics to be included in the final analysis. We do not have a specific sample size, and the statistical models will be adapted to the event rate provided by the sample recruited.

However, a minimum sample size is estimated, expecting 50% of patients with at least one complication-which are the data that require a larger sample size-with a confidence level of 95% and an accuracy of 3%, of a total of 3012 patients. The larger the sample size, the more accurate it will be. So, it is intended to recruit the largest possible number of centres and patients.

Table 3. Explanatory data variables collected for POWER.2

Patient	Pharmacological	Surgical	Laboratory
<ul style="list-style-type: none"> • Age • Gender • BMI • ASA Score • Smoking status • Hypertension • Diabetes mellitus • Coronary arterial disease • Stroke • COPD/Asthma • Atrial fibrillation • Peripheral arterial disease • CHADS2-VASc score • Clinical frailty scale 	Anti-aggregants and anticoagulants (type, daily dose and the time at which the drug was withdrawn until surgery)	<ul style="list-style-type: none"> • Surgery time • Intraoperative blood loss • Intraoperative diuresis • Intraoperative fluid administration (including type of fluid) • Surgical approach • Surgical technique • Time of ischaemia • Intraoperative fluid balance • Use of surgical drain 	<ul style="list-style-type: none"> • Haemoglobine • Albumin • Creatinine • Glicaemia • Glycosilated haemoglobin • Ferritine • Transferrine Saturation • C-reactive protein • Vit B12

BMI: body mass index; ASA: American Society of Anesthesiologists physical status classification;
 COPD: chronic obstructive pulmonary disease; CHADS2-VASc: estimates stroke risk in patients with atrial fibrillation. In all patients, the fluid balance is calculated as follows: administered fluids (including crystalloid, colloid and blood products) – (estimated bleeding + insensible losses* + diuresis) *1.5 mL kg⁻¹ h⁻¹

Table 4. Patient blood management variables

Preoperative	Intraoperative	Postoperative
<ul style="list-style-type: none"> • Preoperative Hb • Preoperative RBC transfusion • Preoperative iron treatment (dose, time, type) • Preoperative epoetin (dose, time, type) • Preoperative Hb after optimisation • Preoperative autodonation 	<ul style="list-style-type: none"> • Tranexamic acid administration (dose, route) (antifibrinolytics) • RBC transfusion • Intraoperative RBC cell saver 	<ul style="list-style-type: none"> • Postoperative Hb • Postoperative iron treatment (dose, time, type) • Postoperative tranexamic acid • Postoperative epoetin (dose, time, type) • Postoperative RBC cell saver

Hb: haemoglobine; RBC: red blood cell

Table 5. Analgesia variables

	THR _s	TKR _s
General Spinal Epidural		
Regional Periarticular injections Peri-incisional	<ul style="list-style-type: none"> • Femoral nerve block • Sciatic nerve block • Shutter nerve block • Fascia iliaca block • Lumbar plexus block • Paravertebral block 	<ul style="list-style-type: none"> • Femoral nerve block • Sciatic nerve block • Adductor canal block • Lumbar plexus block • Paravertebral block

Catheter utilisation will be evaluated for regional anaesthesia techniques (epidural, regional, periarticular and paraincisional)

We will analyse outcomes depending on whether the patient belonged to an ERAS programme as declared by the hospital where the intervention will be performed. The discrete

and continuous variables will be described as n (%) and median (P₂₅-P₇₅) and their differences analysed using the Fisher or Pearson and Wilcoxon tests respectively. Subsequently, we

will repeat the analysis, subdividing the sample into quartiles according to the real compliance rate of the ERAS items, and comparing the quartiles of higher and lower compliance and calculating a linear fit of the compliance with the variable under study. Next, we will analyse the complications rate for each of the ERAS items using the Fisher test and will perform a multivariate analysis to study the influence in the rate of each of the items together with the clinical and demographic variables. Finally, we will apply the Kaplan-Meier test to determine whether there were differences in-hospital and critical care length of stay depending on the patient's inclusion in an ERAS programme or the ERAS compliance quartile. To avoid errors by multiple comparisons, we will calculate the respective q-value for each p-value to maintain a false discovery rate below 5%. We will admit as statistically significant those comparisons where the p-value and q-value are below 0.05.

Excel 2010 will be used for data handling, and statistical modelling will be conducted in SPSS V.22.

Methods for minimising bias

All patients will be consecutively screened, and if found to be eligible, informed consent will be obtained. The number of screened, included and analysed patients will be reported, and differences will be explained.

Preoperative data capturing and outcome assessment will be performed by two different investigators. Statistical analysis will be performed after the database closure.

Statistical measurements such as imputation will be taken to minimise the risk of bias due to incomplete outcome data. The results of this study will be prepared in accordance with guidelines set by the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement for observational studies (11).

To avoid the risk of selective reporting, the trial protocol with full information about outcomes and variables is hereby published. Any financial relationship or any conflict of interest that could inappropriately influence the work within this project will be stated explicitly. Confounding will be minimised by inclusion of covariates and factors in the statistical analysis of the primary end point.

Additional analyses and data sharing

We have developed a process for enabling us to consider requests from investigators outside the Steering Committee to conduct secondary analyses on POWER.2 data. This includes formal consideration by the POWER.2 project team and steering committees using a predefined standard data sharing request form.

Ethical approval

Ethical approval for this study has been obtained from the Comité de Ética de la Investigación de la Comunidad Autónoma de Aragón (C.P.-C.I. PI18/135; on 23 May 2018). It was registered on 27 June 2018 at www.clinicaltrials.gov with identification no. NCT03570944. Local ethical approval will be required at each participating centre. Although this study has no impact on clinical practice, informed consent will be requested for all participants. Patient data will be treated in accordance with the European General Data Protection Regulation 2016/679. The study protocol, technical appendix and other documents are available on www.grupogerm.es/power2.

Project management

The POWER.2 Steering Committee will be responsible for protocol development, data collection and data analysis. A structured system of regional and local leadership has been created to coordinate the POWER.2 study. Regional leads will recruit, advise and ensure the correct approvals are in place for each hospital within their region. Local leads will oversee data collection in their hospital, ensuring adherence to local governance protocols and continuous data collection.

Results

Dissemination

The protocol will be disseminated through the Spanish Perioperative Audit and Research Network (RedGERM), the Spanish Society of Anaesthesia and Critical Care (SEDAR) and the 'Grupo Español de Rehabilitación Multimodal' (GERM). All protocol documents and relevant clinical toolkits will be made available through the POWER.2 website (www.grupogerm.es/power2). Individual unit data will be presented at local meetings. Overall collective data will be published in peer-reviewed journals. It is anticipated that the results from this prospective study will help inform ongoing clinical research and will be used to inform commissioning and implement changes within the Spanish National Health Service.

Discussion

Currently, there is no agreed consensus on the optimal perioperative strategy in patients undergoing elective THRs and TKRs. Due to the large differences in the number and nature of the individual elements included in the ERAS programmes, the incomplete information in the studies, the lack of standardisation in the ERAS programmes and the lack of agreement on what constitutes an ERAS protocol, there is little evidence about which specific protocol elements are those that are associated independently with improvements in the postoperative outcome. Although this occurs in other

surgical disciplines, it is especially important in orthopaedic surgery. Overall, a high level of participation is expected at the national level, which is why the data obtained will make it possible to clearly establish the key ERAS elements as well as the patients who will benefit most from the ERAS protocol and, on the other hand, identify those areas in which more research is needed.

Our study is, to the best of our knowledge, novel for investigating current perioperative management in patients undergoing elective THRs and TKRs and its subsequent impact on clinical outcomes with collaborative support from orthopaedic surgeons and anaesthetists. Moreover, we hope to reach a high number of patients included in a very short period of time, which makes the data obtained more reliable. We also will investigate current Patient Blood Management (PBM) programme influences in the ERAS programme. Preoperative anaemia is quite frequent in these patients, and even if mild, it is associated with worse outcomes (12). We will analyse the impact of PBM measures on the improvement of ERAS programme benefits.

Conclusion

The data generated from this prospective, multicentre and observational cohort study will help to identify and plan future research areas, evaluate the efficacy of ERAS protocols in the elective practice of THRs and TKRs, develop a consensus on appropriate clinical endpoints and accumulate data for the generation of power calculations to develop future randomised controlled trials.



You can reach the supplementary material of this article at <https://doi.org/10.5152/TJAR.2019.87523>

Ethics Committee Approval: Ethics committee approval was received for this study from the research ethics committee of Comunidad Autónoma de Aragón, Spain (C.P.-C.I. PI18/135; on 23 May 2018).

Informed Consent: Written informed consent was obtained from patients who participated in this study.

Peer-review: Externally peer-reviewed.

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Supplementary Table 1. Predefined mild-moderate-severe overall postoperative complications according EPCO definitions		
Complication	Definition	Graduation
Acute Kidney Injury	<ul style="list-style-type: none"> - <i>Mild</i>: Serum creatinine increase of 1.5-1.9 times baseline value within 7 days or $\geq 0.3 \text{ mg dL}^{-1}$ ($30 \mu\text{mol L}^{-1}$) within 48 hours. Urine output $\leq 0.5 \text{ mL kg}^{-1} \text{ h}^{-1}$ for 6-12 hours. - <i>Moderate</i>: Serum creatinine increase of 2.0-2.9 times baseline value within 7 days. Urine output $\leq 0.5 \text{ mL kg}^{-1} \text{ h}^{-1}$ for 12 hours. - <i>Severe</i>: Serum creatinine increase of 3.0 times baseline within 7 days or increase in serum creatinine to $\geq 4.0 \text{ mg dL}^{-1}$ ($\geq 350 \mu\text{mol L}^{-1}$) with an acute rise of $>0.5 \text{ mg dL}^{-1}$ ($>50 \mu\text{mol L}^{-1}$) or initiation of renal replacement therapy. Urine output $\leq 0.3 \text{ mL kg}^{-1} \text{ h}^{-1}$ for 24 hours or anuria for 12 hours. 	<ul style="list-style-type: none"> • Included in definition
Acute Respiratory Distress Syndrome (ARDS)	Respiratory failure, or new or worsening respiratory symptoms, commencing within 1 week of surgery; a chest radiograph or computed tomography scan which demonstrates bilateral opacities not fully explained by effusions, lobar/lung collapse, or nodules; and respiratory failure not fully explained by cardiac failure or fluid overload. Needs objective assessment (e.g. echocardiography) to exclude hydrostatic oedema if no risk factors present.	<ul style="list-style-type: none"> - <i>Mild</i>: $\text{PaO}_2:\text{FiO}_2$ between 200 and 300 mmHg with PEEP or CPAP $\geq 5 \text{ cmH}_2\text{O}$ - <i>Moderate</i>: $\text{PaO}_2:\text{FiO}_2$ between 100 and 200 mmHg with PEEP $\geq 5 \text{ cmH}_2\text{O}$ - <i>Severe</i>: $\text{PaO}_2:\text{FiO}_2 \leq 100 \text{ mmHg}$ with PEEP $\geq 5 \text{ cmH}_2\text{O}$
Pneumonia	<p>Chest radiographs with new or progressive and persistent infiltrates, or consolidation, or cavitation, and at least one of the following:</p> <ol style="list-style-type: none"> a) Fever ($>38^\circ\text{C}$) with no other recognised cause b) Leukopenia (<4000 white blood cells/mm^3) or leucocytosis ($>12,000$ white blood cells/mm^3) c) For adults >70 years old, altered mental status with no other recognised cause... and at least two of the following: <ul style="list-style-type: none"> - New onset of purulent sputum or change in character of sputum, or increased respiratory secretions, or increased suctioning requirements - New onset or worsening cough, or dyspnoea, or tachypnoea - Râles or bronchial breath sounds - Worsening gas exchange (hypoxia, increased oxygen or ventilator demand) 	<ul style="list-style-type: none"> - <i>Mild</i>: Results in only temporary harm and would not usually require specific clinical treatment. - <i>Moderate</i>: More serious complication, but one which does not usually result in permanent harm or functional limitation. Usually requires clinical treatment. - <i>Severe</i>: Results in significant prolongation of hospital stay and/or permanent functional limitation or death. Almost always requires clinical treatment.
Cardiac arrest	The cessation of cardiac mechanical activity, as confirmed by the absence of signs of circulation. Electrocardiograph (ECG) changes may corroborate the incidence of cardiac arrest.	<ul style="list-style-type: none"> • None: Binary (yes/no)
Arrhythmia	ECG evidence of cardiac rhythm disturbance.	<ul style="list-style-type: none"> - <i>Mild</i>: Results in only temporary harm and would not usually require specific clinical treatment. - <i>Moderate</i>: More serious complication, but one which does not usually result in permanent harm or functional limitation. Usually requires clinical treatment. - <i>Severe</i>: Results in significant prolongation of hospital stay and/or permanent functional limitation or death. Almost always requires clinical treatment.

Supplementary Table 1. Predefined mild-moderate-severe overall postoperative complications according EPCO definitions (continued)		
Complication	Definition	Graduation
Deep vein thrombosis	A new blood clot or thrombus within the venous system. Systematic screening is required in trials in which DVT is an important outcome measure. Appropriate diagnostic tests include ultrasound, venography, CT or MRI venography.	<ul style="list-style-type: none"> - <i>Mild</i>: Results in only temporary harm and would not usually require specific clinical treatment. - <i>Moderate</i>: More serious complication, but one which does not usually result in permanent harm or functional limitation. Usually requires clinical treatment. - <i>Severe</i>: Results in significant prolongation of hospital stay and/or permanent functional limitation or death. Almost always requires clinical treatment.
Stroke	Embolic, thrombotic, or haemorrhagic cerebral event with persistent residual motor, sensory or cognitive dysfunction (e.g. hemiplegia, hemiparesis, aphasia, sensory deficit, impaired memory).	<ul style="list-style-type: none"> - <i>Mild</i>: Results in only temporary harm and would not usually require specific clinical treatment. - <i>Moderate</i>: More serious complication, but one which does not usually result in permanent harm or functional limitation. Usually requires clinical treatment. - <i>Severe</i>: Results in significant prolongation of hospital stay and/or permanent functional limitation or death. Almost always requires clinical treatment.
Pulmonary oedema	Evidence of fluid accumulation in the alveoli due to poor cardiac function	<ul style="list-style-type: none"> - <i>Mild</i>: Results in only temporary harm and would not usually require specific clinical treatment. - <i>Moderate</i>: More serious complication, but one which does not usually result in permanent harm or functional limitation. Usually requires clinical treatment. - <i>Severe</i>: Results in significant prolongation of hospital stay and/or permanent functional limitation or death. Almost always requires clinical treatment.
Pulmonary embolism	A new blood clot or thrombus within the pulmonary arterial system. Guidance: Appropriate diagnostic tests include scintigraphy and CT angiography. Plasma D-dimer measurement is not recommended as a diagnostic test in the first 3 weeks following surgery.	<ul style="list-style-type: none"> - <i>Mild</i>: Results in only temporary harm and would not usually require specific clinical treatment. - <i>Moderate</i>: More serious complication, but one which does not usually result in permanent harm or functional limitation. Usually requires clinical treatment. - <i>Severe</i>: Results in significant prolongation of hospital stay and/or permanent functional limitation or death. Almost always requires clinical treatment.
Surgical site infection (superficial)	Infection involving only superficial surgical incision which meets the following criteria: 1) Infection occurs within 30 days after surgery. 2) Infection involves only skin and subcutaneous tissues of the incision. 3) The patient has at least one of the following: a) Purulent drainage from the superficial incision b) Organisms isolated from an aseptically obtained culture of fluid or tissue from the superficial incision and at least one of the following signs or symptoms of infection: pain or tenderness, localised swelling, redness, or heat, or superficial incision is deliberately opened by surgeon and is culture positive or not cultured. A culture-negative finding does not meet this criterion. c) Diagnosis of an incisional surgical site infection by a surgeon or attending physician	<ul style="list-style-type: none"> - <i>Mild</i>: Results in only temporary harm and would not usually require specific clinical treatment. - <i>Moderate</i>: More serious complication, but one which does not usually result in permanent harm or functional limitation. Usually requires clinical treatment. - <i>Severe</i>: Results in significant prolongation of hospital stay and/or permanent functional limitation or death. Almost always requires clinical treatment.

Supplementary Table 1. Predefined mild-moderate-severe overall postoperative complications according EPCO definitions (continued)		
Complication	Definition	Graduation
Surgical site infection (deep)*	An infection which involves both superficial and deep parts of surgical incision and meets the following criteria: 1) Infection occurs within 30 days after surgery if no surgical implant is left in place or 1 year if an implant is in place. 2) The infection appears to be related to the surgical procedure and involves deep soft tissues of the incision (e.g. fascial and muscle layers). 3) The patient has at least one of the following: a) Purulent drainage from the deep incision but not from the organ/space component of the surgical site b) A deep incision spontaneously dehisces or is deliberately opened by a surgeon and is culture positive or no cultures were taken whilst the patient has at least one of the following signs or symptoms of infection: fever (>38°C) or localised pain or tenderness. A culture-negative finding does not meet this criterion. c) An abscess or other evidence of infection involving the deep incision is found on direct examination, during surgery, or by a histopathologic or radiologic examination d) Diagnosis of a deep incisional surgical site infection by a surgeon or attending physician	<ul style="list-style-type: none"> - <i>Mild</i>: Results in only temporary harm and would not usually require specific clinical treatment. - <i>Moderate</i>: More serious complication, but one which does not usually result in permanent harm or functional limitation. Usually requires clinical treatment. - <i>Severe</i>: Results in significant prolongation of hospital stay and/or permanent functional limitation or death. Almost always requires clinical treatment.
Surgical site infection (organ/space)	An infection which involves any part of the body excluding the fascia or muscle layers and meets the following criteria: 1) Infection occurs within 30 days after surgery. 2) The infection appears to be related to the surgical procedure and involves any part of the body, excluding the skin incision, fascia, or muscle layers, that is opened or manipulated during the operative procedure. 3) The patient has at least one of the following: a) Purulent drainage from a drain that is placed through a stab wound into the organ/space b) Organisms isolated from an aseptically obtained culture of fluid or tissue in the organ/ space c) An abscess or other evidence of infection involving the organ/space that is found on direct examination, during reoperation, or by histopathologic or radiologic examination d) Diagnosis of an organ/space surgical site infection by a surgeon or attending physician	<ul style="list-style-type: none"> - <i>Mild</i>: Results in only temporary harm and would not usually require specific clinical treatment. - <i>Moderate</i>: More serious complication, but one which does not usually result in permanent harm or functional limitation. Usually requires clinical treatment. - <i>Severe</i>: Results in significant prolongation of hospital stay and/or permanent functional limitation or death. Almost always requires clinical treatment.
Bloodstream infection	An infection which is not related to infection at another site and which meets either of the following criteria: 1) Patient has a recognised pathogen cultured from blood cultures which is not related to an infection at another site. 2) Patient has at least one of the following signs or symptoms: fever (>38°C), chills, or hypotension and at least one of the following: a) Common skin contaminant cultured from two or more blood cultures drawn on separate occasions b) Common skin contaminant cultured from at	<ul style="list-style-type: none"> - <i>Mild</i>: Results in only temporary harm and would not usually require specific clinical treatment. - <i>Moderate</i>: More serious complication but one which does not usually result in permanent harm or functional limitation. Usually requires clinical treatment. - <i>Severe</i>: Results in significant prolongation of hospital stay and/or permanent functional limitation or death. Almost always requires clinical treatment.

Supplementary Table 1. Predefined mild-moderate-severe overall postoperative complications according EPCO definitions (continued)		
Complication	Definition	Graduation
	least one blood culture from a patient with an intravascular line, and a physician starts antimicrobial therapy c) Positive blood antigen test	
Myocardial infarction	Increase in serum cardiac biomarker values (preferably cardiac troponin) with at least one value above the 99th percentile upper reference limit and at least one of the following criteria: - Symptoms of ischaemia - New or presumed new ST-segment or T-wave ECG changes or new left bundle branch block - Development of pathological Q-waves on ECG - Radiological or echocardiographic evidence of new loss of viable myocardium or new regional wall motion abnormality - Identification of an intra-coronary thrombus at angiography or autopsy	<ul style="list-style-type: none"> - <i>Mild</i>: Results in only temporary harm and would not usually require specific clinical treatment. - <i>Moderate</i>: More serious complication, but one which does not usually result in permanent harm or functional limitation. Usually requires clinical treatment. - <i>Severe</i>: Results in significant prolongation of hospital stay and/or permanent functional limitation or death. Almost always requires clinical treatment.
Urinary tract infection	An infection associated with at least one of the following signs or symptoms which should be identified within a 24-hour period: fever (>38°C), urgency, frequency, dysuria, suprapubic tenderness, costovertebral angle pain or tenderness with no other recognised cause and a positive urine culture of ≥105 colony-forming units/mL with no more than two species of microorganisms.	<ul style="list-style-type: none"> - <i>Mild</i>: Results in only temporary harm and would not usually require specific clinical treatment. - <i>Moderate</i>: More serious complication, but one which does not usually result in permanent harm or functional limitation. Usually requires clinical treatment. - <i>Severe</i>: Results in significant prolongation of hospital stay and/or permanent functional limitation or death. Almost always requires clinical treatment.
Paralytic ileus	Failure to tolerate solid food or defecate for three or more days after surgery	<ul style="list-style-type: none"> - <i>Mild</i>: Results in only temporary harm and would not usually require specific clinical treatment. - <i>Moderate</i>: More serious complication, but one which does not usually result in permanent harm or functional limitation. Usually requires clinical treatment. - <i>Severe</i>: Results in significant prolongation of hospital stay and/or permanent functional limitation or death. Almost always requires clinical treatment.
Delirium	Delirium may be identified using the Intensive Care Delirium Screening Checklist. Patients are first evaluated for an altered level of consciousness. Those with a response to mild or moderate stimulation, an exaggerated response to stimulation or normal wakefulness are evaluated fully. Patients receive one point for each of the following criteria: inattention, disorientation, hallucination-delusion-psychosis, psychomotor agitation or retardation, inappropriate speech or mood, sleep-wake cycle disturbance or symptom fluctuation.	<ul style="list-style-type: none"> • Integrated into definition
Postoperative haemorrhage	Blood loss occurring within 72 hours after the end of surgery, which would normally result in transfusion of blood.	<ul style="list-style-type: none"> - <i>Mild</i>: Any sign of haemorrhage (any bleeding that is more than expected, including bleeding only identified by an imaging study), that does not meet criteria for type moderate-severe but requires at least one of the following points: • Non-surgical medical intervention by a health professional (examples include stopping antiplatelet,

Supplementary Table 1. Predefined mild-moderate-severe overall postoperative complications according EPCO definitions (continued)		
Complication	Definition	Graduation
		<p>antithrombotic medication, compression at the bleeding site, use of drugs to reverse the effect such as protamine and vitamin K).</p> <ul style="list-style-type: none"> • Requires hospitalisation or increased level of care • Requires prompt evaluation with tests such as blood count, urinalysis, coagulation tests, endoscopy and tomography <p>- <i>Moderate:</i></p> <ul style="list-style-type: none"> • Bleeding with a decrease in haemoglobin from ≥ 3 to <5 g dL⁻¹ (related to bleeding) • Any need for transfusion due to obvious bleeding • Decrease in haemoglobin ≥ 5 g dL⁻¹ (related to bleeding) • Bleeding that requires surgical intervention for its control • Bleeding that requires the use of vasoactive agents <p>- <i>Severe</i></p> <ul style="list-style-type: none"> • Transfusion of ≥ 5 units of red blood cells, within a period of 48 hours; fatal bleeding

Supplementary Table 2. Definitions and stratification of TKRs complications		
Complication	Definition	Graduation
Neural deficit	Postoperative neural deficit (sensory or motor)	<ul style="list-style-type: none"> - <i>Mild</i>: Results in only temporary harm and would not related to the index TKR usually require specific clinical treatment. - <i>Moderate</i>: More serious complication, but one which does not usually result in permanent harm or functional limitation. Usually requires clinical treatment. - <i>Severe</i>: Results in significant prolongation of hospital stay and/or permanent functional limitation or death. Almost always requires clinical treatment
Vascular injury	Intraoperative vascular injury requiring surgical repair, bypass grafting, or stenting (compartment syndrome or amputation should be reported)	<ul style="list-style-type: none"> - <i>Mild</i>: Not applicable - <i>Moderate</i>: Complication requires unplanned surgical treatment, prolonged hospital admission or readmission (surgical treatment and/or admission) - <i>Severe</i>: The complication is associated with an event that threatens the limb or puts life-threatening, which requires immediate invasive treatment; or it leads to the death of the patient
Medial collateral ligament injury	Intraoperative or early postoperative medial collateral ligament injury requiring repair, reconstruction, a change in prosthetic constraint, revision surgery, or TKA protocol	<ul style="list-style-type: none"> - <i>Mild</i>: The complication does not require treatment and has no clinical relevance; there is no deviation from routine follow-up; the therapeutic regimens allowed include: antiemetics, antipyretics, analgesics, diuretics, electrolytes, antibiotics (without treatment) or a slight change in care with a low-intensity outpatient treatment (non-surgical treatment) - <i>Moderate</i>: Complication requires unplanned surgical treatment, prolonged hospital admission or readmission (surgical treatment and/or admission) - <i>Severe</i>: The complication is associated with an event that threatens the limb or puts life-threatening, which requires immediate invasive treatment; or it leads to the death of the patient
Instability	Symptomatic instability reported by the patient and confirmed by laxity on physical examination as defined by The Knee Society Knee Score	<ul style="list-style-type: none"> - <i>Mild</i>: The complication does not require treatment and has no clinical relevance; there is no deviation from routine follow-up; the therapeutic regimens allowed include: antiemetics, antipyretics, analgesics, diuretics, electrolytes, antibiotics (without treatment) or a slight change in care with a low-intensity outpatient treatment (non-surgical treatment) - <i>Moderate</i>: Complication requires unplanned surgical treatment, prolonged hospital admission or readmission (surgical treatment and/or admission) - <i>Severe</i>: The complication is associated with an event that threatens the limb or puts life-threatening, which requires immediate invasive treatment; or it leads to the death of the patient
Malalignment	ESymptomatic misalignment reported by the patient and confirmed radiographically with angular deformity in the coronal plane >10° from the mechanical axis	<ul style="list-style-type: none"> - <i>Mild</i>: Not applicable - <i>Moderate</i>: Surgery required - <i>Severe</i>: In case the reoperation leads to more complications
Stiffness	Limited ROM as reported by the patient and demonstrated in a physical examination with extension limited to 15° short of full extension or flexion <90° (not applicable if preoperative arc of motion <75°)	<ul style="list-style-type: none"> - <i>Mild</i>: Not applicable - <i>Moderate</i>: Surgery required - <i>Severe</i>: In case the reoperation leads to more complications

Supplementary Table 2. Definitions and stratification of TKRs complications (continued)		
Complication	Definition	Graduation
Deep periprosthetic joint infection	A deep periprosthetic joint infection can be diagnosed when there is a sinus tract communicating with the prosthesis; or a pathogen is isolated by culture from at least two separate tissue or fluid samples obtained from the affected prosthetic joint; or four of the following six criteria exist: elevated ESR and serum CRP concentration; elevated synovial WBC count; elevated synovial PMN; presence of purulence in the affected joint; isolation of a microorganism in one culture of periprosthetic tissue or fluid; or >5 neutrophils/high-power field in five high-power fields observed from a histologic analysis of periprosthetic tissue at ×400 magnification	<ul style="list-style-type: none"> - <i>Mild</i>: Not applicable - <i>Moderate</i>: Successfully treated infection - <i>Severe</i>: If resection arthroplasty or permanent disability or death occurs
Periprosthetic fracture	Periprosthetic fracture of the distal femur, proximal tibia, or patella (operative or nonoperative treatment should be recorded)	<ul style="list-style-type: none"> - <i>Mild</i>: Not applicable - <i>Moderate</i>: Surgery required - <i>Severe</i>: In case the reoperation leads to more complications
Extensor mechanism disruption	Disruption of the extensor mechanism (surgical repair and/or extensor lag should be recorded) -	<ul style="list-style-type: none"> - <i>Mild</i>: Not applicable - <i>Moderate</i>: Surgery required - <i>Severe</i>: In case the reoperation leads to more complications
Patellofemoral dislocation	Dislocation of the patella from the femoral trochlea (direction of instability should be recorded)	<ul style="list-style-type: none"> - <i>Mild</i>: Not applicable - <i>Moderate</i>: Surgery required - <i>Severe</i>: In case the reoperation leads to more complications
Tibiofemoral dislocation	Dislocation of the tibiofemoral joint (direction of instability should be recorded)	<ul style="list-style-type: none"> - <i>Mild</i>: Not applicable - <i>Moderate</i>: Surgery required - <i>Severe</i>: In case the reoperation leads to more complications
Bearing surface wear	Wear of the bearing surface symptomatic or requiring reoperation	<ul style="list-style-type: none"> - <i>Mild</i>: Not applicable - <i>Moderate</i>: Surgery required - <i>Severe</i>: In case the reoperation leads to more complications
Osteolysis	Expansile lytic lesion adjacent to one of the implants ≥1 cm in any one dimension or increasing in size on serial radiographs/CT scans	<ul style="list-style-type: none"> - <i>Mild</i>: Not applicable - <i>Moderate</i>: Surgery required - <i>Severe</i>: In case the reoperation leads to more complications
Implant loosening	Implant loosening confirmed intraoperatively or identified radiographically as a change in implant position or a progressive, radiolucent line at the bone-cement or bone-implant interface	<ul style="list-style-type: none"> - <i>Mild</i>: Not applicable - <i>Moderate</i>: Surgery required - <i>Severe</i>: In case the reoperation leads to more complications
Implant fracture or tibial insert dissociation	Implant fracture or dissociation of the tibial insert from the tibial implant	<ul style="list-style-type: none"> - <i>Mild</i>: Not applicable - <i>Moderate</i>: Surgery required - <i>Severe</i>: In case the reoperation leads to more complications
Reoperation	Return to the operating room related to the index TKRs	<ul style="list-style-type: none"> - <i>Mild</i>: Not applicable - <i>Moderate</i>: Surgery required - <i>Severe</i>: In case the reoperation leads to more complications
Revision	Revision of one or more of the TKA implants (femur, tibia, tibial insert, patella)	<ul style="list-style-type: none"> - <i>Mild</i>: Not applicable - <i>Moderate</i>: Surgery required - <i>Severe</i>: In case the reoperation leads to more complications

ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; WBC: white blood cell count; PMN: polymorphonuclear cells

Supplementary Table 3. Definitions and stratification of THRs complications		
Complication	Definition	Graduation
Neural deficit	Postoperative neural deficit (sensory or motor) related to the index THR (ICD-9 997.09)	<ul style="list-style-type: none"> - <i>Mild</i>: Results in only temporary harm and would not usually require specific clinical treatment. - <i>Moderate</i>: More serious complication, but one which does not usually result in permanent harm or functional limitation. Usually requires clinical treatment. - <i>Severe</i>: Results in significant prolongation of hospital stay and/or permanent functional limitation or death. Almost always requires clinical treatment
Vascular injury	Intraoperative vascular injury requiring surgical repair, bypass grafting, or stenting (compartment syndrome or amputation should be reported)	<ul style="list-style-type: none"> - <i>Mild</i>: Not applicable - <i>Moderate</i>: Complication requires unplanned surgical treatment, prolonged hospital admission or readmission (surgical treatment and/or admission) - <i>Severe</i>: The complication is associated with an event that threatens the limb or is life-threatening, which requires immediate invasive treatment, or it leads to the death of the patient
Dislocation/instability	Dislocation of the femoral head out of the acetabulum or recurrent symptomatic subluxation of the hip	<ul style="list-style-type: none"> - <i>Mild</i>: The complication does not require treatment and has no clinical relevance; there is no deviation from routine follow-up; the therapeutic regimens allowed include antiemetics, antipyretics, analgesics, diuretics, electrolytes, antibiotics (without treatment) or a slight change in care with a low-intensity outpatient treatment (non-surgical treatment) - <i>Moderate</i>: Complication requires unplanned surgical treatment, prolonged hospital admission or readmission (surgical treatment and/or admission) - <i>Severe</i>: The complication is associated with an event that threatens the limb or is life-threatening, which requires immediate invasive treatment, or it leads to the death of the patient
Abductor muscle disruption	Symptomatic abductor dysfunction, which was not present before the operation, associated with positive Trendelenburg sign and use of an ambulatory assist (cane, crutch, walker) for treatment of limp or weakness	<ul style="list-style-type: none"> - <i>Mild</i>: Not applicable - <i>Moderate</i>: Surgery required - <i>Severe</i>: In case the reoperation leads to more complications
Heterotopic ossification	Symptomatic heterotopic ossification at 1 year after operation associated with stiffness, reduced ROM and radiographic grade of Brooker III or IV	<ul style="list-style-type: none"> - <i>Mild</i>: Not applicable - <i>Moderate</i>: Surgery required - <i>Severe</i>: In case the reoperation leads to more complications
Deep periprosthetic joint infection	A deep periprosthetic joint infection can be diagnosed when there is a sinus tract communicating with the prosthesis; or a pathogen is isolated by culture from at least two separate tissue or fluid samples obtained from the affected prosthetic joint; or four of the following six criteria exist: elevated ESR and serum CRP concentration, elevated synovial WBC count; elevated synovial PMN; presence of purulence in the affected joint; isolation of a microorganism in one culture of periprosthetic tissue or fluid; or >5 neutrophils/high-power field in five high-power fields observed from histologic analysis of periprosthetic tissue at x400 magnification	<ul style="list-style-type: none"> - <i>Mild</i>: Not applicable - <i>Moderate</i>: Successfully treated infection - <i>Severe</i>: If resection arthroplasty or permanent disability or death occurs
Periprosthetic fracture	Periprosthetic fracture of the proximal femur or the acetabulum	<ul style="list-style-type: none"> - <i>Mild</i>: Not applicable - <i>Moderate</i>: Surgery required

Supplementary Table 3. Definitions and stratification of THRs complications (continued)		
Complication	Definition	Graduation
		- <i>Severe</i> : In case the reoperation leads to more complications
Implant fracture	Implant fracture	- <i>Mild</i> : Not applicable - <i>Moderate</i> : Surgery required - <i>Severe</i> : In case the reoperation leads to more complications
Bearing surface wear	Wear of the bearing surface symptomatic or requiring reoperation	- <i>Mild</i> : Not applicable - <i>Moderate</i> : Surgery required - <i>Severe</i> : In case the reoperation leads to more complications
Osteolysis	Expansile lytic lesion adjacent to one of the implants ≥ 1 cm in any one dimension or increasing in size on serial radiographs/CT scans	- <i>Mild</i> : Not applicable - <i>Moderate</i> : Surgery required - <i>Severe</i> : In case the reoperation leads to more complications
Implant loosening	Implant loosening confirmed intraoperatively or identified radiographically as a change in implant position or a progressive radiolucent line at the bone-cement or bone-implant interface	- <i>Mild</i> : Not applicable - <i>Moderate</i> : Surgery required - <i>Severe</i> : In case the reoperation leads to more complications
Cup liner dissociation	Dissociation of the cup liner from the acetabular shell	- <i>Mild</i> : Not applicable - <i>Moderate</i> : Surgery required - <i>Severe</i> : In case the reoperation leads to more complications
Reoperation	Return to the operating room related to the index TKRs	- <i>Mild</i> : Not applicable - <i>Moderate</i> : Surgery required - <i>Severe</i> : In case the reoperation leads to more complications
Revision	Revision of one or more of the TKA implants (femur, tibia, tibial insert, patella)	- <i>Mild</i> : Not applicable - <i>Moderate</i> : Surgery required - <i>Severe</i> : In case the reoperation leads to more complications
ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; WBC: white blood cell count; PMN: polymorphonuclear cells		