Computer Navigation in Total Knee Replacement Surgery

Effect on Outcome

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Dissertation for the degree philosophiae doctor (PhD)

at the University of Bergen

2013

Dissertation date: 29.11.2013

Scientific environment

This thesis is part of a research project investigating computer navigation in total knee replacement surgery, performed during 2005-2013 at the Norwegian Arthroplasty Register, in close collaboration with the University of Bergen, Department of Clinical Medicine, and the four Norwegian hospitals; Haugesund Hospital, Haugesund Sanitetsforening's Hospital of Rheumatic Diseases, Haukeland University Hospital and Lovisenberg Deaconal Hospital. The research was led and supervised by Professor Ove Furnes, MD/PhD (UiB). Local co-supervisor was Sigbjørn Berentsen, MD/PhD at Haugesund Hospital.

The project was funded by the Norwegian Research Council (NRC) and included a PhD fellowship (received by the author). The four hospitals mentioned above have supported the project by infrastructure and a clinical research environment. The author received the Smith & Nephew award for this project in 2008, granted by the Norwegian Orthopedic Association.

The author has been employed at the Department of Orthopedics, Haugesund Hospital, Helse Fonna HF, during the entire research period.

The thesis is a part of the PhD program at the Department of Clinical Medicine, University of Bergen.

Contents

Acknowledgements

I am grateful to be part of a scientific environment combining research and clinical activities. Thanks to all the people involved, and in particular I would like to thank:

Supervisor, project leader:

Ove Furnes (Professor, Orthopedic surgeon, MD/PhD). Thank you, for excellent support and education. Your infinite energy and optimism has pushed me through this project, and you have taught me many lessons during my PhD education. I am grateful that you believed in me and gave me the opportunity to take part in this knee project. The foundation is laid, and I look forward to the continuation of our research.

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Research staff:

Norwegian Arthroplasty Register:

Lasse Engesæther (leader of the register), Ove Furnes (responsible for the Knee Arthroplasty Register), Leif Ivar Havelin (responsible for the Hip Arthroplasty Register), Tor Egil Sørås/Kjersti Steindal (IT support, establishing the database), Gro Dyrhovden (radiographic analysis), Birgitte Espehaug (statistical support), Anne Marie Fenstad (statistical support). Thanks to all the people working at the register for your excellent support. It has been a great pleasure for me to be part of this research environment.

Clinical research unit for adults:

Kristine Stadheim (data registry, radiographic analysis), Toril Våge (data registry), Hilde Sælensminde (data registry)

Local support at Haugesund Hospital:

Kari Heggland (local coordinator)

Sigbjørn Berentsen (local co-supervisor: Hematologist, PhD/MD)

Eirik Dankel (IT-support, figures)

Doris Gundersen (help and support in the application process for financial support)

Local support at Haukeland University Hospital:

Janneke Korsvold (depersonalizing and processing radiographic images into the database)

Anne-Lise Salbu (local coordinator)

Innovest AS:

Ingun Heie Anundskås (monitor), Ingfrid Titlestad (economy)

Radiographers:

Terje Stokke (Haukeland University Hospital), Jan Sørbø (Haugesund Hospital), Alf Trygve Velde (Haugesund Hospital), Chedli Jemli (Haugesund Hospital), Siri Hemset (Lovisenberg Deaconal Hospital). Thank you all for your patience, creative solutions and a great job with the radiography.

Radiologists (Haukeland University Hospital):

Svein Halvorsen, Per Martin Kristoffersen, Eivind Strøm. Thank you for your valuable contributions in adapting and developing the radiological protocol.

Surgeons:

Haukeland University Hospital: Ove Furnes, Geir Hallan, Claus Jacobsen, Arne Skredderstuen

Lovisenberg Hospital: Tore Jervidalo, Gunnar Petursson

Haugesund Sanitetsforening's Hospital for Rheumatic Diseases (HSR): Herman Luhr (Thank you for valuable tips and tricks, for backing me up in the operating theatre and for facilitating the collaboration with HSR)

Haugesund Hospital: Øystein Gøthesen

Scientific collaborators:

Paul Johan Høl (Post-Doc Research Fellow at Laboratory of Bio-materials, University of Bergen, PhD, review and scientific contributions)

Other research/clinical support:

Johan Dahlstrøm (sales manager at Smith & Nephew, sharing valuable knowledge and providing education, door opener, facilitator)

Emil Mohr (Orthopedic surgeon, MD, my boss for 10 years at Haugesund Hospital, who led me into orthopedics/principles of surgery with experience and wisdom)

Øystein Høvik (Orthopedic surgeon, MD, leader of the orthopedic department at Lovisenberg Deaconal Hospital, taking part in the design of the multi-center RCT, inspiring us and sharing valuable experience)

Gisle Uppheim (Orthopedic surgeon, MD, Lovisenberg Deaconal Hospital, taking part in the design of the multi-center RCT, sharing his great experience)

Anne Hilde Bjøntegård, Hans Jacob Rossebø and Berit Haaland who have been the leaders of the Clinic of Surgery at Haugesund Hospital (includes the Department of Orthopedic Surgery) during the research period from 2007 until today. Thank you for providing a supportive working environment at Haugesund Hospital and for making it possible to combine research and clinical activity.

Physical therapists, nurses and colleagues at Haugesund Hospital, Haugesund Sanitetsforening's Hospital for Rheumatic Diseases, Haukeland University Hospital and Lovisenberg Deaconal Hospital. Thank you for your valuable contributions and positive attitude regarding our clinical trial.

Other economic support:

The foundation "Folkets gave" founded by patients and supporters of Haugesund Sanitetsforening's Hospital for Rheumatic Diseases (financially supporting a local research coordinator of our project)

Personal support:

Thank you, my beloved wife Brit Jorunn, for your vital support through love and kindness.

Thanks to my parents who taught me what life is about, and always supported me.

Thanks to my brothers Harald Andreas and Frode, and to my sister Karianne, and their families, who are always there for me and my family.

Thanks to my beloved children Kristiane, John and Synnøve, who give me joy and meaning in life, every day.

List of abbreviations

ASA - The American Society of Anesthesiologists (ASA) Physical Status classification system

CAS – Computer Assisted Surgery

CEA – Cost-Effectiveness Analysis

CI – 95% Confidence Interval

CON* – Conventionally operated total knee replacement

CONV* – Conventionally operated total knee replacement

CT – Computer Tomography

EQ-5D – Health questionnaire developed by the EuroQol group

ICER – Incremental Cost-Effectiveness Ratio

KM – Kaplan Meier

KOOS – Knee injury and Osteoarthritis Outcome Score

KSS – (American) Knee Society Score

NAR – Norwegian Arthroplasty Register

MRI – Magnetic Resonance Imaging

RCT – Randomized Controlled Trial

RSA – Radiostereometric Analysis (syn. Roentgen Stereophotogrammetric Analysis)

RR – Relative Risk

TKR – Total Knee Replacement

VAS – Visual Analogue Scale

WOMAC – Western Ontario and McMaster Universities Osteoarthritis Index

*When we started planning the research project in 2007, most authors used the abbreviation CON, but later the abbreviation CONV was used. One of our articles uses CON and another article CONV as abbreviation for conventionally operated TKR. Sorry for the inconvenience! In the thesis the abbreviation CONV is preferred, in order to separate from the meaning “against”, as in “pro et contra”.

The term “classical CAS” refers to the image-less CAS using infrared light and reflection beads fixed to the bone by pins in the tibial and femoral shaft.

List of publications

Paper I

Gothesen, O., Slover, J., Havelin, L.I., Askildsen, J., Malchau, H., and Furnes, O. An economic model to evaluate cost-effectiveness of computer assisted knee replacement surgery in Norway. BMC Musculoskelet Disord. 2013 Jul 6;14(1):202.

Paper II

Gothesen, O., Espehaug, B., Havelin, L.I., Petursson, G., Furnes, O. Short term outcome of 1,465 computer-navigated primary total knee replacements 2005-2008. Acta Orthop. 82.3 (2011): 293-300.

Paper III

Gothesen, O., Espehaug, B., Havelin, L.I., Petursson, G., Lygre, S., Ellison, P., Hallan, G., Furnes, O. Survival rates and causes of revision in cemented primary total knee replacement: A report from the Norwegian Arthroplasty Register 1994-2009. Bone Joint J. 95-B.5 (2013): 636-42.

Paper IV

Gothesen, O., Espehaug, B., Havelin, L.I., Petursson, G., Hallan, G., Strøm, E., Dyrhovden, G., and Furnes, O. Functional outcome and alignment in computer assisted and conventionally operated total knee replacements. A multi-centre parallel-group randomized controlled trial. Submitted 2013.

Abstract

Background: In total knee replacement surgery (TKR), the surgeon aims to align the implant according to the mechanical axis of the limb. Among knee surgeons the dominating belief is that good alignment reduces wear and loosening of the implant, and optimizes patellar tracking, range of motion and function of the knee, although the evidence is limited. Computer navigation has been used in total knee replacement surgery for more than a decade to improve the alignment (abbr. CAS – computer assisted surgery). The term "navigation" in this setting refers to positioning of the implant relative to the anatomy of the knee. Conventional (traditional) navigation, or positioning, is performed by the use of intramedullary or extramedullary rods to align the implant according to the mechanical axis of the limb (abbr. CONV – conventional TKR). In contrast, with the classical image-less computer navigation there is no need of intramedullary rods, and image-less computer navigation utilizing infrared cameras and advanced software, is shown to be more accurate than conventional navigation. However, it is costly and time consuming. The purpose of this thesis was to investigate the relationship between use of computer navigation and outcome.

Methods: To what extent this new technology must improve the outcome to become cost-effective, was evaluated in an economic model. One register study analyzes the outcome of computer navigated TKR, another register study investigates the survivorship and revision causes of the most common implant brands, and a randomized clinical trial (RCT) evaluates the functional and radiological outcome of CAS.

Results/discussion: Paper I shows that CAS might be cost-effective in TKR if the hospital volume is high and the cost of the equipment does not increase relative to the prices of today. Age of the patient is not likely to have any influence on cost-effectiveness. However, the cost-effectiveness depends on a marginal improvement of implant survivorship. Based on the findings in paper IV with improved alignment and marginally improved functional scores, there is some reason to be optimistic in

regard to impact on survivorship. On the contrary, the findings in paper II, with increased risk of revision in the short term, suggest that there might not be an improved survivorship with CAS in the long term, at least not the way it has been used in Norway. Results in Norway may differ from the results in other countries and is probably dependent on education of the surgeons in the use of this new technology, and also of the patient volume and thereby the surgeon's experience with CAS. Additionally, the design of the implant and its compatibility with the computer navigation software and hardware, might affect the results as suggested in paper II. To further elucidate this aspect, a register study was performed analyzing revision causes and survivorship of the most used TKR implants in Norway. The mobile-bearing LCS Complete seemed to perform inferiorly when computer navigated, and we suspected that the mobile-bearing design was difficult to navigate properly. To separate the negative effect of computer navigation from other causes of inferior survivorship, we decided to conduct a register study excluding the computer navigated knees, investigating revision causes and survivorship (paper III). Paper III showed that the LCS Complete and the LCS Classic both had a 7-fold increased risk of revision due to aseptic loosening of the tibial components, compared to the most used knee implant in Norway - the Profix knee. Even the femoral component had an increased risk of revision due to aseptic loosening. However, the 5 years Kaplan-Meier survival rates were 94.9 and 95.6 for the LCS Complete and LCS Classic, respectively, compared to 96.3 for the Profix. This difference is by many, not considered clinically significant, but the risk of aseptic loosening is more alarming and proven to be independent of CAS.

The project will continue to evaluate the reasons for aseptic loosening in the LCS knees by collaboration with other national registers and by studying revised and unused implants in the laboratory. The positive results of CAS, in paper IV, urge us to continue the evaluation of this technology as it develops, through repeated register analyses and clinical trials investigating improved types of navigation. The thesis is part of a larger project investigating long term survivorship with radiostereometric analysis and long term follow-ups.

Conclusion: Computer navigation in total knee replacement surgery has increased the operation time and resulted in inferior short term survivorship in Norway. However, the technology is more accurate than conventional technique, and the functional results are marginally improved by CAS. If these positive effects result in a better long term survivorship of the implant, the technology is getting more user-friendly and the operation time is reduced, the technology is likely to be cost-effective and beneficial for the patients.

1. Introduction

1.1 Background:

Osteoarthritis of the knee is a common disease among the elderly, and there are increasing numbers of young patients suffering from degenerative joint disease[1]. The results of total knee replacement (TKR) have improved over the last decades and the health gain is substantial. Consequently, TKR has become a highly cost-effective procedure[2-4]. Patients with end-stage arthritis of the knee are typically offered a TKR. There are many different types of implants, and the quality of a specific implant is evaluated by functional results, risk of complications and risk of revision (implant survivorship) in clinical trials, register studies and retrospective studies[1]. Also, laboratory testing and in vitro studies are performed to evaluate the effect of prosthesis design, surface texture and coating, method of fixation and the impact and usefulness of surgical instruments[5-8]. Furthermore, studies have shown that education, patient volume, patient's expectations, selection of patients and experience of the surgeon affect the outcome of a TKR[9;10].

Computer assisted surgery (CAS) was first introduced to neurosurgery[11] and then later to orthopedic surgery and knee replacement[12;13]. This technology helps the surgeon to "navigate" the implant into its right position. Thus, it is often called "computer navigation". The purpose of using this technology in TKR was to improve alignment of the implant. Alignment refers to the position of the implant relative to the femur and tibia. A well aligned implant is placed with the mechanical axis of the implant in line with the mechanical axis of the limb, in the frontal plane. It was assumed that good (frontal) alignment was related to an increased resistance to wear and aseptic loosening of the implant, and by computer navigation the number of patients getting a malaligned knee, would be reduced. The avoidance of intramedullary rods would possibly reduce bleeding, microemboli (fat) and postoperative delirium, and the technology offered a new tool for balancing of the ligaments[14]. There were concerns about increased costs and operating times, and

some new complications arrived like fracture at the site of marker pins (incidence 0-1.3%)[15-17], pain or infection at the pin site (incidence 1.7%)[18] , software problems and technical errors[19].

Different computer navigation systems were available, CT-based or so-called image-less, closed systems confined to one specific implant, or open systems adaptable to any implant. Software and instruments were adapted and improved over the years. Pin-less computer navigation was developed to avoid the problems with fractures, bleeding and wound problems at the site of the pin fixation. Patient specific cutting blocks were developed as an alternative to CAS, and the most recent development is the accelerometer based navigation technology. However, the classical image-less CAS is still widely used around the world, and the principles of using CAS to improve the alignment of TKR remain the same. The application of these principles to the surgical procedure may vary between surgeons according to the type of CAS being used, software developments and adaptions, traditions, education, experience, implant type and surgical methods. Most surgeons aim to align the implant with the mechanical axis of the limb. However, the ligament balancing technique may vary according to implant type, local tradition and education. The software may be adapted to a “gap balancing technique” or a “measured bone resection technique” (explained later in chapter 1.5), and to fixed bearing and mobile bearing implants. Also, there may be a learning curve with CAS, but even for inexperienced surgeons this instrument might give good results with respect to alignment[20]. The impact of CAS on rotational alignment is still debated as the results are divergent[14;21;22]. Most trials with CAS report no improvement in functional results[23;24]. Thus, an eventual improvement with CAS is more likely to be found in the joint registers and long term follow-ups with regard to survivorship of the implants. A study by Ritter et al from 1994 refers to inferior survivorship for malaligned implants[25], and most orthopedic surgeons believe that good alignment is crucial to reduce wear and shear forces, and to get good long term survival rates.

To investigate the impact of CAS on modern knee implants, we decided to study the results in the Norwegian Arthroplasty Register and in a clinical trial (Paper II/IV). CAS increases the cost of a TKR, so we also wanted to investigate to what extent CAS must improve the results of a TKR, to be cost-effective (Paper I). The results of CAS differed for various implant brands, so we performed a second register study to separate the impact of CAS from the impact of implant brand design, on the long term results (Paper III).

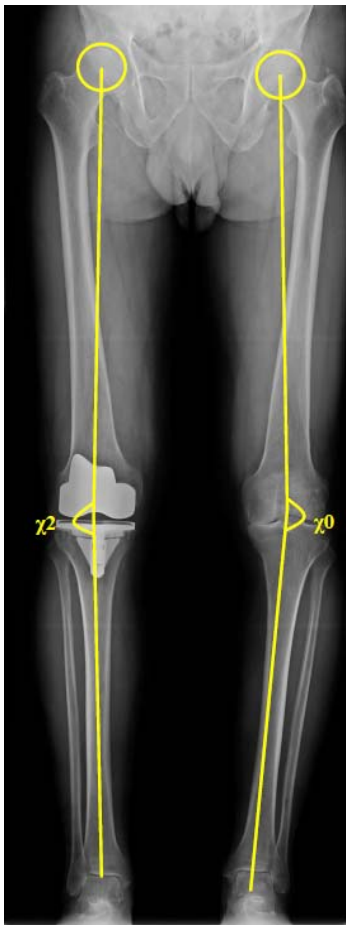

Fig. 1a)

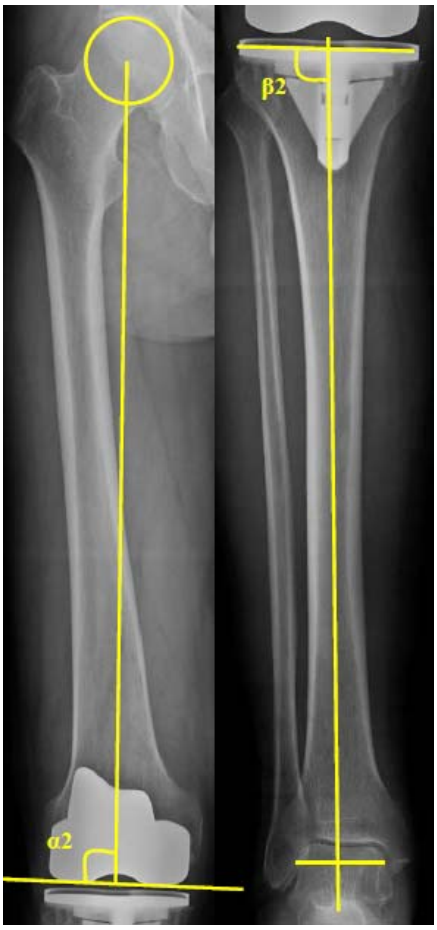

Fig. 1b)

*a) Image on the left showing the limb alignment (Hip-Knee-Ankle angle (χ**))** on full-length radiographs of a prosthetic knee and a non-operated osteoarthritic knee.*

b) Image on the right showing how the prosthesis aligns with the mechanical axis of the femur(α) and tibia (β) separately.

1.2 Computer assisted surgery, the technology

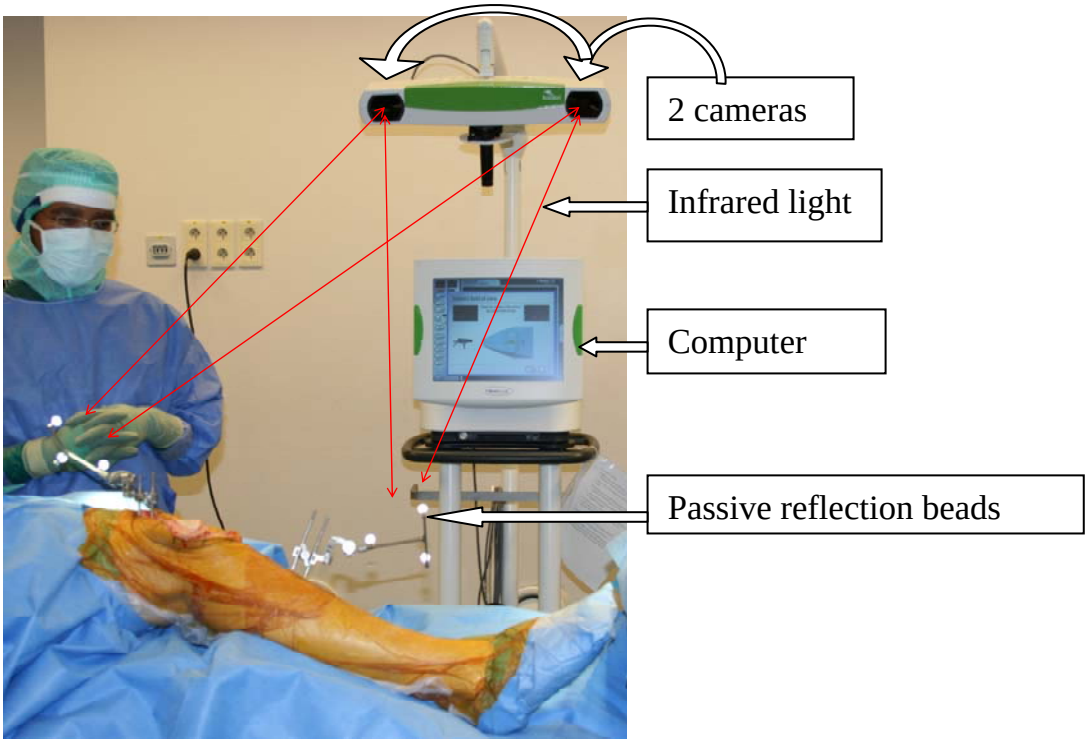

Fig 2. Image illustrating the principles of computer assisted surgery in total knee replacement using an image-less open navigation system from Brainlab (Vectorvision software, the Kolibri model which was used in the RCT).

Classical image-less computer assisted surgery (infrared light).

Two cameras emit infrared light and registers reflected infrared light from three or more beads attached to the tibia and femur (image). The reciprocal distances and movements are measured between the beads in a three dimensional system, and are registered by the computer which builds a model of the extremeties axes and anatomy. Surgical instruments are navigated according to the same principle, and anatomical landmarks are registered by a pointer probe equipped with reflection beads. According to the marked landmarks of the ankle and knee, an axis of the tibia is obtained. To find the axis of the femur, the femur is rotated in a circular pattern. As

the hip joint is not moving during this procedure, the markers will produce circles and the fixed center of the hip can be deducted as the vertex of a cone (Fig. 3).

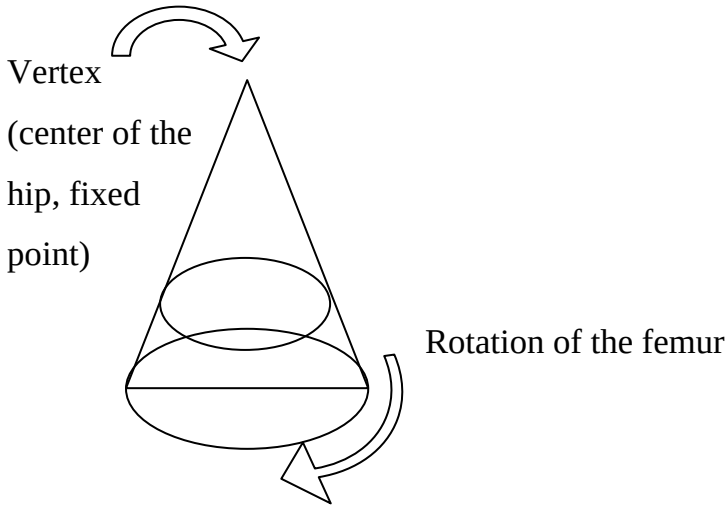

Figure 3. Image illustrating how the computer calculates the center of the hip to obtain the mechanical axis of the femur.

Electromagnetic tracking systems

Electromagnetic tracking systems do not require a camera or a free line of sight. A dynamic reference frame and an electromagnetic transmitter are used in a similar manner as camera and infrared light. Disadvantages are that the trackers are linked to the computer by wires, which might represent obstacles in the surgical field. Another disadvantage is that the electromagnetic signals might be affected by interference with ferromagnetic instruments and other electromagnetic equipment in the operating room[26]. The method has an accuracy within 1.5 degrees in vitro[27], compared to 1 degree with the classical infrared light based CAS[28;29]. Comparable accuracy has been obtained in a clinical setting[30].

Ultrasonic tracking systems

This system has a potential to register anatomic landmarks without perforation of the skin, thus facilitating minimally invasive procedures. However, the method has not

yet been proven to be sufficiently accurate for total knee replacement in a clinical setting. However, the results from a cadaver study showed some promising results[31].

CT-based (image-based) computer assisted surgery

CT-based computer assisted surgery is the most accurate technology, using information on anatomy and axes obtained from CT scans. In total knee replacement surgery however, these systems are largely replaced by the image-less systems proven to be sufficiently accurate and reliable [32].

Fluoro-navigation

Fluoroscopic navigation is of limited value in knee replacement surgery. Partly because of the problems with manipulation of a C-arm in the operating room, potentially threatening the sterility of the procedure, and partly due to the need of lead protection, to protect the staff and the patient from irradiation[31].

Patient specific cutting blocks

An MRI (or CT) of the affected limb (including hip, knee and ankle) contains sufficient information to generate conformed cutting blocks fitting exactly on the arthritic surface of the patient's knee. Osteophytes are parts of the arthritic surface and should not be removed until the cuts have been made. The cutting blocks are made by the manufacturer, based on information from the MRI. The surgeon plans the alignment and position of the implant on a computer in his office, and saves the time needed to mark the anatomical landmarks and surfaces during the operation. In other words, the computer navigation is done beforehand, in the office. Another advantage is that the size of the implant is known before surgery. Consequently, the local storage of implants might be reduced. Disadvantages are that the ligament

balancing tool of the classical CAS is no longer an option. The cutting blocks are costly, and an MRI (performed according to a specific protocol) is needed for every patient [33].

Pin-less computer navigation

This is a simplified kind of CAS using the intra- or extramedullary rods as fixation along with fixation of the cutting blocks. The reference array is placed into the cutting guide slot after fixation of the cutting block to check and adjust the alignment. In addition anatomical landmarks are marked (the same as for traditional CAS), but no surface registration is needed. The advantages are the possibility to fine-tune the alignment[34], and the avoidance of fixation pins in the tiba and femur with potential complications like fracture, pin site pain or pin site infection (occurring in 1.3-1.7% of cases)[15;17;18]. Disadvantages are that ligament balancing and sizing of the implant is no longer possible with this system, and the intramedullary canal is violated.

Accelerometer based computer assisted surgery

Accelerometers are used to register anatomical landmarks and obtaining mechanical axes. The advantages reported are that the system is small and portable, it does not require extra pin sites for the reflection beads on tibia and femur, and it does not require an intraoperative line of sight between the infrared cameras and the reflection beads [35]. One disadvantage is that it does not allow an intraoperative accuracy check of the bone cuts. The system “KneeAlign” (OrthAlign, Aliso Viejo, California, USA) is approved for clinical use by the FDA, and according to the manufacturer more than 10 000 surgeries have been performed using this product, in the USA, Europe and Australia (personal correspondence with Erika Rojas, marketing & sales coordinator).

1.3 Implant designs

Knee replacement started with pure molded inlays and plates of metal. Among the pioneers were Campbell in 1940 [36], and the Norwegian born orthopedic surgeon, Smith Petersen in 1942 [37]. Various implants of different materials and design were tested until the prototype of modern TKRs (total condylar knee) was promoted by Insall et al in 1972 [38-40]. Since then, the production methods and materials have developed, and more anatomic models have been introduced to improve the outcome for the patients. Every manufacturer of TKRs will insist that their design is unique, and in fact they are, but the differences are often minimal. The undersurface, geometry and texture of the implants are different and the shape of the stem or keel varies. However, only minor changes to the implant may change the fate from success to failure [41;42]. It is generally accepted, in the literature and in the arthroplasty registers, to separate into mobile-bearing and fixed bearing implants. Among the fixed bearings, most authors distinguish modular fixed bearing from non-modular fixed bearing (often called mono-block). Furthermore, there is a various extent of constraint of the implant, from the fully constrained hinged implant to no constraint at all. Another issue of debate is whether the surgeon ought to resurface the patella. In the United States patella resurfacing is regularly performed as a part of the TKR procedure. In Europe however, patella resurfacing is generally not considered necessary for most patients [43;44]. However, the Australian Joint Replacement Registry showed that there was a lower risk of revision for posterior cruciate stabilized (PS) knees when patella resurfacing had been performed[45]. This difference is probably due to different traditions, implants used, and health systems. Additionally, due to unique designs, all manufacturers make their own surgical instruments for implantation of the prosthesis, which in turn will affect the outcome. Good surgical instruments are of course important to achieve good results. Computer navigation is a surgical instrument, and it may be implant specific (closed system) or universal (open system). Consequently, quality of software and hardware, as well as adaption to surgical instruments and various prosthesis brands, are likely to affect the results of computer navigated TKR.

1.4 Fixation methods

The prosthetic implants of today are fixed to the bone, either by the use of cement or by bony in-growth to the implant (called cementless). The cement is based on PMMA (polymethylmethacrylate) and for primary joint replacements most surgeons in Europe prefer cement containing antibiotics to reduce the risk of infection [46;47]. Cementless fixation is obtained by making the surface rough or textured by different methods. Often the implant is textured by blasting, or coated by small beads and/or hydroxy-apatite, or the metal structure is made highly porous, to facilitate bony in-growth. Some metals are proven to be tissue friendly allowing bony in-growth, like titanium and tantalum. Primary total knee replacements in Norway are predominantly performed with antibiotic-loaded cement (80% of femoral components and 90% of tibial components in 2011) [48].

1.5 Surgical techniques to achieve optimal position in total knee replacement

Implantation of the prosthesis in alignment with the mechanical axis of the limb is by most surgeons accepted as the optimal positioning of the implant in the frontal (coronal) plane. However, there is some debate on whether patients with constitutional varus position of the knees are to be fully corrected when getting a TKR [49]. In the lateral (sagittal) plane there is no general agreement on what is the optimal position. Whiteside et al showed that a posterior slope of the tibial plateau was important for range of motion, and even flexing the femoral component to improve condylar lift-off in deep flexion, may increase range of motion and increase stability [50]. In the axial plane the optimal rotational position of the implant is debatable. Some surgeons argue that the optimal rotation is parallel to the transepicondylar axis. Then the patella tracking is aligned with the mechanical axis of the femur throughout the whole range of motion. In surgery this axis is hard to define, and Dr.. Leo Whiteside found that the trochlear groove of the femur was oriented

perpendicular to this axis [51]. Thus, a “Whiteside’s line” (trochlear anteroposterior axis) may be drawn in the deepest part of the trochlear groove to find the transepicondylar axis, indirectly. Then the bone-cuts are made according to this line. A technique using a reference axis of the femur (derived from bony landmarks) is often referred to as a “measured bone resection technique”. On the other hand, the ligaments are important stabilizers of the knee joint, and some surgeons emphasize that the ligaments ought to guide the rotational position of the implant, and that this technique is more reliable than the use of bony landmarks [52]. The tibia cut is done first, perpendicular to the tibial mechanical axis, and then the posterior femoral condyles resection is performed according to the so-called “gap balancing technique”. The ligaments are tightened with the knee in a flexed position, and the bone resection is done to create a rectangular gap with equal tension medially and laterally. Both techniques have been clinically tested and there is no clear evidence that one of these techniques is superior to the other [53]. We decided to use the technique described by Leo Whiteside in our clinical trial, since all the participating hospitals in the clinical trial use this technique as their standard of choice [54].

1.6 Implant brands investigated

The most used implant brands in primary total knee replacement surgery in Norway the last decade were: LCS Complete and LCS Classic (mobile bearing, DePuy), Profix (fixed modular bearing, Smith & Nephew), Duracon (fixed modular bearing, Stryker), and NexGen (fixed modular bearing, Zimmer), AGC Universal and AGC Anatomic (fixed non-modular bearing (mono-block), Biomet). (Details are given in the supplement to paper III). In addition the E-motion knee from Aesculap was included for analysis in paper II, as this was one of the most frequently computer navigated TKRs.

2. Aims of the studies

Based on data from the Norwegian Arthroplasty Register and a parallel-group randomized controlled trial, the aims of the studies were to:

1. Evaluate the cost-effectiveness of computer navigation in total knee replacement surgery for two age cohorts, various patient volumes and various costs.

2. Assess short term survivorship, operation time and complications of computer navigated TKR in Norway during 2005-2008.

3. Evaluate revision causes and survivorship in cemented primary TKRs in Norway during 1994-2009. Focus on brand specific features and design categories (mobile-bearing, fixed modular/non-modular bearing).

4. Compare CAS and CONV in total knee replacement surgery by functional outcome, radiological outcome (alignment/positioning), survivorship, operation time, complications and bleeding, in a randomized controlled multi-center trial.

3. Methods

3.1 Paper I

3.1.1 Economic evaluation

By employing a Markov model, we analyzed the cost-effectiveness of computer assisted surgery versus conventional arthroplasty with respect to implant survival and operation volume in two theoretical Norwegian age cohorts; 60-year-olds and 75-year-olds. We obtained mortality and hospital cost data over a 10-year period from Norwegian registers and extrapolated to 20 years. We presumed that the cost of an intervention would need to be below NOK 500,000 per QALY (Quality Adjusted Life Year) gained, to be considered cost effective.

The relative profitability of two alternative technologies, computer assisted and conventional surgery, was established using a cost-effectiveness analysis. This type of comparison needs to consider possible changes to both benefits and costs. New technology may be cheaper or more expensive, and may have a better or worse impact compared to traditional technology. If computer assisted surgery proved to be cheaper and better, or poorer and more expensive, the solution would be trivial, since one technology would be dominant. However, with the introduction of CAS, both costs and benefits might increase. Hence, there was a need of deliberation. This is normally presented in the form of an incremental cost-effectiveness ratio – ICER, i.e. an equation showing the change in cost relative to the change in effect for the two alternatives. This provides a cost per unit of benefit gained, which in turn may be compared to society's demand for useful employment of resources. In Norway, common practice uses a threshold value of NOK 500,000 for acceptable cost per quality-adjusted life year gained [55]. This does not mean that every intervention that scores below the threshold value should necessarily be accepted. It is also necessary to consider the intervention in relation to the resources available. Consequently, it is important to clarify the perspective of the analysis - patient, healthcare enterprise or

society. Our analysis considered the benefits and costs from the point of view of a healthcare enterprise, whilst more indirect social costs, to relatives for instance, or the cost of absence from work, were excluded.

The measure of benefit is a quality-adjusted life year. The utility values used here have been calculated by means of EQ-5D, a standardized questionnaire (developed by the EuroQol Group) which includes the five dimensions of mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension has three levels – no problems, some problems, extreme problems. By establishing the number of years during which patients experience the different utility values, we arrive at quality-adjusted life years. In turn these can be summarized for a patient population, in order to find the total benefit levels (measure of benefit) to be compared against the costs.

3.1.2 The Markov model

A Markov decision model is used to analyze various matters in a number of cycles (20 years in this model). In our model, a cycle lasted one year. We looked at the probability of certain occurrences, such as revision and death, within each cycle. Since each occurrence had an associated probability, this probability could be used to calculate the relevant costs and utility values within the same cycle.

Costs and utility values were allocated to each primary procedure and revision procedure. In this model, the patients went from one health state to another at an age-specific frequency and probability based on Norwegian data sources. The theoretical patient cohort accumulated costs and utility values over time. Based on the Markov model, we deduced total costs and quality-adjusted life years to evaluate the cost effectiveness of conventional surgical techniques and computer assisted surgery. The model was constructed with the use of a decision analysis software (TreeAge Pro 2009, Williamstown, MA).

Implant survival

For patients over and under the age of 70 stipulations were made for implant survival and yearly probability of revision within the two cohorts, based on data from the Norwegian and Swedish Arthroplasty Registers and large-scale cohort studies.

Probability of death

The probability of death within the first year, including perioperative death, was based on linked data from the Norwegian Arthroplasty Register and the National Population Register of Norway for 60 and 75-year-olds.

Utility values

Patients who receive a TKR are expected to have the same quality of life on completion of the postoperative phase and rehabilitation period whether their surgery was conventional or computer assisted. The utility values used in the model were based on findings from previous publications evaluating arthroplastic surgery [56;57].

Disutility value

The disutility value represents the reduced quality of life experienced by the patient in connection with a particular health state or clinical outcome. The disutility value was only allocated to the first post-operative year.

Costs

The added cost of computer navigation includes expenditure such as computer hardware and knee replacement software, instruments and maintenance contracts (prices from Brainlab). The annual cost was divided by the number of patients operated, in order to find the added cost per operation. Frequent upgrades and new technology may be envisaged to drive the costs up. Consequently, we also looked at the outcome in a scenario where prices were increased by 100%. The cost per operation, without the use of computer navigation, was based on Diagnosis Related

Group (DRG) rate 209A for primary prostheses and 209B for revision prostheses, in 2011.

3.1.3 Decision analysis

The ICER (”incremental cost-effectiveness ratio”) was found by dividing the difference between total accumulated costs (including the cost of future knee replacement revisions) by the difference in total quality-adjusted life years gained for each of the surgical methods. As in accordance with the guidance provided by the UK National Institute for Clinical Excellence (NICE), our calculations did not include loss of productivity [58]. The total cost and total number of quality-adjusted life years were analyzed for each of the surgical methods (CAS and CONV) when all patients included in the model had reached the health state of dead. A two-way sensitivity analysis was used for the two age cohorts in order to investigate the relationship between patient volume, the probability of revision, and the cost effectiveness of computer assisted surgery in Norway (Additional file to paper I, table C and table D).

3.1.4 Ethics (CEA)

The Norwegian Arthroplasty Register has permission from the Norwegian Data Inspectorate to collect patient data, based on obtaining written consent from patients (last issued May 24, 2004; reference number 2003/58-3).

3.2 Paper II

3.2.1 Prospective observational register study (CAS-study)

Primary knee replacements reported to the Norwegian Arthroplasty Register during the period 2005–2008 were included in this prospective observational study. The register was established in 1987 as a hip replacement register [59]. The registration of knee replacements started in 1994 [60], but the use of computer navigation was not registered until 2005. At the time of surgery, a form is completed and sent to the register (Appendix 1) including information on age, sex, laterality, ASA category, date of surgery, preoperative diagnosis, previous knee surgery, prosthesis type and brand, prophylactic antibiotics, antithrombotic medication, approach (minimally invasive or not), surgical method (use of computer navigation or not, and the name of the system being used), fixation method, intraoperative complications, status of the cruciate ligaments, and whether the present operation was a primary or secondary (revision) procedure. Revision is defined as a complete or partial removal/exchange of the implant, or insertion of a component (including patella button). Primary operations were linked to subsequent revisions by the unique identification number of all Norwegian residents. Of all knee replacements performed in Norway, 99% of all primary operations and 97% of all revisions are estimated to be reported to the register [61].

3.2.2 Inclusion (CAS-study)

11,576 non-patella resurfaced primary total knee replacements implanted during the years 2005–2008 were split into 2 groups: CAS and CONV. Patella resurfaced knee replacements were excluded from the material due to low numbers (9 in the CAS group and 241 in the CONV group). We selected the 3 most frequently used navigation systems (Brainlab, Orthopilot, and Stryker), along with the 5 most frequently used computer-navigated implants (AGC/Biomet; Duracon/Stryker; e.motion/Aesculap, LCS Complete/DePuy; and Profix/Smith & Nephew), leaving 1,465 computer-navigated knees suitable for evaluation.

In the CONV group only the same prosthesis brands as in the CAS group, were selected, giving 8,214 CONV knee replacements for comparison.

3.2.3 Statistics (CAS-study)

Descriptive analyses were performed to assess baseline characteristics of the study groups. Differences were evaluated using the chi-square test for proportions and the independent-samples t-test for mean values. The CONV group was compared to the CAS group regarding survivorship. Revision for any reason, and secondly, revision due to specific causes, were used as endpoints. Median follow-up was calculated following the reverse Kaplan-Meier method [62]. The Kaplan-Meier method provided unadjusted estimates of survivorship after 1 and 2 years of follow-up. The Cox multiple regression model was used to calculate hazard rate ratios (RRs) for evaluation of the effect of computer navigation on survivorship, with adjustment for potential confounding by age (continuous), sex, ASA category (I, II, III/IV), method of fixation (cemented, uncemented, or hybrid cementation (uncemented femur, cemented tibia)), prosthesis brand, preoperative diagnosis (osteoarthritis, other diagnoses), and previous knee surgery (yes/no). In sub-analyses, results of computer-navigated and conventionally operated knees were obtained for each prosthesis brand and also according to fixation method (cemented knee replacements, uncemented knee replacements, and hybrid knee replacements). In a sub-analysis, a possible effect of a learning curve was investigated by excluding the first 20 operations with CAS at each center. The specific results of each center were investigated and the impact of hospital volume was addressed in a separate sub-analysis, by selecting centers with more than 50 CAS cases. Furthermore, a selection of centers performing both operating techniques in the same time period was analyzed. The mean follow-up time was 1.4 years in the CAS group and 1.8 years in the CONV group.

3.2.4 Ethics (CAS-study)

See chapter 3.1.4.

3.3 Paper III

3.3.1 Prospective observational register study (design-study)

Data from patients registered in the NAR during 1994-2009 were evaluated. Any complete or partial removal/exchange of the implant, or insertion of a component (including a patellar component), was considered a revision procedure.

3.3.2 Inclusion (design-study)

All TKRs were cemented and inserted without patellar components. Differences between the designs were predominantly on the tibial side; two were mobile-bearing TKRs (LCS Classic and LCS Complete (DePuy, Warsaw, Indiana), both rotating platform), two were non-modular fixed bearing TKRs (AGC Universal and AGC Anatomic; both Biomet, Warsaw, Indiana), and three were modular fixed-bearing TKRs (Duracon; Stryker, Portage, Michigan; NexGen; Zimmer, Warsaw, Indiana; and Profix; Smith & Nephew, Memphis, Tennessee). The mobile-bearing TKRs were posterior cruciate ligament (PCL) sacrificing, and the others were PCL retaining. Implant designs not in use after 2004, and those that were used in < 500 cases, were excluded. TKRs introduced with computer-navigation were excluded because the technique was not widely used for the TKRs that were selected. Posterior-stabilized implants were excluded because of relatively low numbers (the Profix Conforming Plus was regarded as posterior stabilized). The inclusion criteria were met by 2118 AGC Universal, 1190 AGC Anatomic, 1090 Duracon, 778 NexGen, 6276 Profix, 2606 LCS Classic and 3714 LCS Complete TKRs.

3.3.3 Statistics (design-study)

Revision for any cause was the primary endpoint. Specific causes for revision and types of revision were secondary outcomes. Descriptive analyses were used to assess the baseline characteristics of the various brands. Information on deaths or emigrations up to 31 December 2009 was retrieved from the National Population Register. The survival times of unrevised TKRs were taken at the last date of observation (date of death or emigration, or 31 December 2009). Median follow-up

was calculated with the reverse Kaplan–Meier method. Unadjusted survival curves for the various brands were constructed using the Kaplan-Meier method, and stopped when < 50 knees remained at risk. Survival percentages after five and ten years' follow-up are reported. Cox's multiple regression model was used to calculate hazard rate ratios (RR), adjusted for potential confounding by age, gender, pre-operative diagnose (osteoarthritis or other diagnoses) and previous knee surgery (yes/no). A sub-analysis was performed to present the risk estimates of the category of design relative to fixed modular-bearing designs.

3.3.4 Ethics (design-study)

See chapter 3.1.4

3.4 Paper IV

3.4.1 Randomized controlled trial (RCT)

Interventions

Patients were randomly parallel-group assigned to CAS or CONV (allocation ratio 1:1). Eight surgeons performed the knee replacements. They were all experienced in total knee replacement (performed > 100 CONVs), and each surgeon had done at least 10 total knee replacements with the use of CAS before recruiting patients into the trial. A cemented Profix total knee prosthesis (Smith & Nephew) was implanted in all patients (Figure 4), using Palacos R+G cement (Heraeus, Hanau, Germany). Of the two dominating techniques in total knee replacement, “measured bone resection” and “gap balancing” [52;63], we chose to perform the “measured bone resection” technique in all cases to equalize the groups. The principles of total knee replacement taught by Leo Whiteside were applied [64]. No patella resurfacing was performed. The tibial component was implanted with the aim of a 4 degrees posterior slope. In the CONV group traditional instruments and intramedullary rods were used, and the femoral component was inserted in a neutral alignment in the frontal plane (referring to the mechanical axis, the surgeon could choose between 5° and 7° cutting blocks with reference to the intramedullary rod) and the sagittal plane (referring to the anatomical axis), or optionally with a 4 degrees flexion of the femoral component. In the CAS group, a neutral alignment was aimed for in the frontal plane, and an individualized flexion of the femoral component was allowed in the sagittal plane. The tibial component implantation aimed at 4° posterior slope. Two 4 millimeter bi-cortical pins were drilled into the femur and tibia to affix the reflection beads. The pins into the femur were placed inside the main incision, but the pins into the tibia were placed distal to the main incision with two minor stab incisions. For the purpose of blinding, patients in the CONV group got sham incisions to mimic these stab incisions. The CAS technology used was the VectorVision knee software version 1.6.93616, with the Kolibri system from BrainLAB, Munig, Germany. All patients started weight bearing and walking exercises the first postoperative day. A

standardized exercise program was carried out for all patients postoperatively, and the patients were taught how to exercise on their own after discharge. Tranexamic acid 10 mg/kg was administered intravenously 10 minutes before surgery, and was repeated 10 minutes before release of the tourniquet, to reduce blood loss. No drains were applied to the operated knee, and the knee was positioned in a supine figure of four (90 flexion of the operated knee) for two hours, to minimize bleeding. Antithrombotic medication was administered 4 hours postoperatively and once daily for 17 days (40 mg enoxaparin for subcutaneous injection). Antibiotic medication was administered intravenously within 30 minutes before surgery, after 4 hours, 8 hours and 12 hours, as a prophylaxis against infection (cephalotin 2 g x 4). The skin incision was closed with agraffes.

CT-controlled multi-center study

To our knowledge, this is the largest CT controlled randomized trial performed on this topic. This multi-center study involved 8 surgeons from 4 institutions, providing good external validity of the results.

3.4.2 Inclusion (RCT)

Due to a slow recruitment rate, the age criterion for inclusion was changed after 6 months from 60-80 years to 50-85 years. Eligible patients were 50-85 years old, in need of a total knee replacement, male and female, with osteoarthritis or arthritic disease of the knee, ASA category 1-3 (The American Society of Anesthesiologists (ASA) Physical Status classification system). Exclusion criteria were severe systemic disease, severe neurological disorder, a history of cancer, dementia, body mass index > 35, previous shaft fractures of the tibia or femur, severe valgus position of the knee (> 15 degrees from the mechanical axis of the knee), previous osteotomy of the tibia or femur, recent knee injury (less than a year preoperatively), severe stiffness of the ipsi-lateral hip, ipsi-lateral hip replacement, and allergy to metals. For patients in need of two knee replacements, only the knee first evaluated in the recruitment period

was included in the trial. Recruitment period was 2009-2011, and patients were recruited from orthopedic clinics at four hospitals in Norway; Haukeland University Hospital (public/Bergen), Lovisenberg Diakonal Hospital (private non-profit/Oslo), Haugesund Hospital (public/Haugesund) and Haugesund Sanitetsforening's Hospital for Rheumatic Diseases (private non-profit/Haugesund).

3.4.3 Statistics (RCT)

Primary outcome was functional scores (Knee Society Score (KSS), Knee injury and Osteoarthritis Outcome Score (KOOS), EQ-5D and Visual Analogue Scale (VAS)) after 3months and 1 year. Secondary outcomes were alignment and positioning of the implant, operation time and bleeding. CT scans were performed 3 months after surgery. In addition, full-length radiographs were performed preoperatively and 3 months after surgery. Frontal alignment of the operated limb was measured on full-length radiographs as the angle from the center of the hip, through the center of the knee and to the center of the ankle. For CT-scans this outcome was the sum of the frontal alignments of the femoral component and the tibial component. The radiographic measures were performed by 4 specially trained assistants (1 nurse, 1 medical student and 2 radiologists) according to a specific protocol (Appendix 13). To compare mean angles, means and mean improvements of the KSS, KOOS, EQ-5D, VAS (Appendices 3-11) and changes in hemoglobin values, we used independent samples t-tests with 95% confidence intervals. Differences in outliers, age, Charnley category, sex, side and diagnosis were assessed by the Pearson Chi-square test. All tests were two-sided. A p-value > 0.05 was considered statistically significant. The software package IBM SPSS Statistics 20, was used in all analyses and calculations. The correlation of radiological measurements performed by different radiologists was assessed by Intraclass Correlation Coefficient (ICC2), [65].

3.4.4 Ethics (RCT)

The trial was approved by the Regional committee for medical and health research

ethics, Bergen September 29, 2007 (ref.no:2007/12587-ARS), and registered in the public database “Clinical trials” October 30, 2008 (ref.no: NCT00782444).

Figure 4. Profix total knee implant, non-porous for use with cement, with keel stem.

4. Summary of papers

Paper I

Background: The use of Computer Assisted Surgery (CAS) for knee replacements is intended to improve the alignment of knee prostheses in order to reduce the number of revision operations. Is the cost effectiveness of computer assisted surgery influenced by patient volume and age?

Methods: By employing a Markov model, we analyzed the cost effectiveness of computer assisted surgery versus conventional arthroplasty with respect to implant survival and operation volume in two theoretical Norwegian age cohorts. We obtained mortality and hospital cost data over a 20-year period from Norwegian registers. We presumed that the cost of an intervention would need to be below NOK 500,000 per QALY (Quality Adjusted Life Year) gained, to be considered cost effective.

Results: The added cost of computer assisted surgery, provided this has no impact on implant survival, is NOK 1037 and NOK 1414 respectively for 60 and 75-year-olds per quality-adjusted life year at a volume of 25 prostheses per year, and NOK 128 and NOK 175 respectively at a volume of 250 prostheses per year. Sensitivity analyses showed that the 10-year implant survival in cohort 1 needs to rise from 89.8% to 90.6% at 25 prostheses per year, and from 89.8 to 89.9% at 250 prostheses per year for computer assisted surgery to be considered cost effective. In cohort 2, the required improvement is a rise from 95.1% to 95.4% at 25 prostheses per year, and from 95.10% to 95.14% at 250 prostheses per year.

Conclusion: The cost of using computer navigation for total knee replacements may be acceptable for 60-year-old as well as 75-year-old patients if the technique increases the implant survival rate just marginally, and the department has a high operation volume. A low volume department might not achieve cost-effectiveness unless computer navigation has a more significant impact on implant survival, and may defer the investments until such data are available.

Paper II

Background: Improvement of positioning and alignment by the use of computer-assisted surgery (CAS) might improve longevity and function in total knee replacements, but there is little evidence. In this study, we evaluated the short-term results of computer-navigated knee replacements based on data from the Norwegian Arthroplasty Register.

Methods: Primary total knee replacements without patella resurfacing, reported to the Norwegian Arthroplasty Register during the years 2005–2008, were evaluated. The 5 most common implants and the 3 most common navigation systems were selected. Cemented, uncemented, and hybrid knees were included. With the risk of revision for any cause as the primary endpoint and intraoperative complications and operating time as secondary outcomes, 1,465 computer-navigated knee replacements (CAS) and 8,214 conventionally operated knee replacements (CON) were compared. Kaplan-Meier survival analysis and Cox regression analysis with adjustment for age, sex, prosthesis brand, fixation method, previous knee surgery, preoperative diagnosis, and ASA category were used.

Results: Kaplan-Meier estimated survival at 2 years was 98% (95% confidence interval (CI): 97.5–98.3) in the CON group and 96% (CI: 95.0– 97.8) in the CAS group. The adjusted Cox regression analysis showed a higher risk of revision in the CAS group (RR = 1.7, CI: 1.1–2.5; p = 0.02). The LCS Complete knee had a higher risk of revision with CAS than with CON (RR = 2.1, CI: 1.3–3.4; p = 0.004)). The differences were not statistically significant for the other prosthesis brands. Mean operating time was 15 min longer in the CAS group.

Conclusion: With the introduction of computer-navigated knee replacement surgery in Norway, the short-term risk of revision has increased for computer-navigated replacement with the LCS Complete. The mechanisms of failure of these implantations should be explored in greater depth, and in this study we have not been able to draw conclusions regarding causation.

Paper III

Background: We evaluated the rates of survival and cause of revision of seven different brands of cemented primary total knee replacement (TKR) in the Norwegian Arthroplasty Register during the years 1994 to 2009.

Methods: Revision for any cause, including resurfacing of the patella, was the primary endpoint. Specific causes of revision were secondary outcomes. Three posterior cruciate-retaining (PCR) fixed modular-bearing TKRs, two fixed non-modular bearing PCR TKRs and two mobile-bearing posterior cruciate-sacrificing TKRs were investigated in a total of 17 782 primary TKRs.

Results: The median follow-up for the implants ranged from 1.8 to 6.9 years. Kaplan-Meier 10-year survival ranged from 89.5% to 95.3%. Cox's relative risk (RR) was calculated relative to the fixed modular-bearing Profix knee (the most frequently used TKR in Norway), and ranged from 1.1 to 2.6. The risk of revision for aseptic tibial loosening was higher in the mobile-bearing LCS Classic (RR = 6.8 (CI: 3.8-12.1)), the LCS Complete (RR = 7.7 (CI: 4.1-14.4)), the fixed modular bearing Duracon (RR = 4.5 (CI: 1.8-11.1)) and the fixed non-modular bearing AGC Universal TKR (RR = 2.5 (CI: 1.3-5.1)), compared with the Profix. These implants (except AGC Universal) also had an increased risk of revision for femoral loosening (RR = 2.3 (CI: 1.1-4.8), RR = 3.7 (CI: 1.6-8.9), and RR = 3.4 (CI: 1.1-11.0), respectively).

Conclusion: These results suggest that aseptic loosening is related to design in TKR.

Paper IV

Background: Comparing the impact of conventional surgical technique (CONV) and computer assisted surgery (CAS) on functional outcome and limb alignment, in total knee replacement surgery.

Methods: A parallel-group randomized controlled trial. 4 Norwegian hospitals, during 2009-2011. Patients aged 55-85 years (n=192, male:female 72:120), with osteoarthritis or arthritic disease of the knee, ASA category 1-3, randomly assigned to CONV (n=95) or CAS (n=97). A central randomization office performed computer-generated allocation to total knee replacement with CONV or CAS. Intention to treat analysis involved 182 patients at 3 months, and 175 patients at 1 year, for functional outcome, and 189 patients for alignment measures. Changes in functional scores (primary outcome) were evaluated after 3 and 12 months. Alignment of the prosthesis (secondary outcome) was analyzed by computer tomography scans and full-length standing radiographs. Patients, nurses, physical therapists, research assistants and outcome assessors were blinded to group assignment. Blinding procedure included sham incisions.

Results: Improvement of functional outcome was inferior for CONV compared to CAS at 3 months follow-up; the Knee Society function score (mean difference (md) 5.9, CI: 0.3-11.4, p=0.039), the Knee injury and osteoarthritis outcome score (KOOS) subscales for “pain” (md: 7.7, CI: 1.7-13.6, p=0.012), “sport” (md: 13.5, CI: 5.6-21.4, p=0.001) and “quality of life” (md: 7.2, CI: 0.1-14.3, p=0.046), and at 1 year follow-up; KOOS “sport” (md: 11.0, CI: 3.0-19.0, p=0.007) and “symptoms” (md: 6.7, CI: 0.5-13.0, p=0.035). There were more outliers (>3° malalignment) with CONV vs CAS concerning frontal alignment of the entire prosthesis (37.9% vs 17.9%, p=0.042), and frontal and sagittal alignment of the tibial component (28.4% vs 6.3%, p=0.002 and 58.9% vs 26.3%, p<0.001). Operation time was 20 minutes longer with CAS. Complications in 9 patients included deep infection (2 CONVs, 1 CAS), superficial infection (1 CONV, 1 CAS), arthrofibrosis (1 CONV), fractures (1 CAS, 2 CONVs) and lung embolism (1 CONV).

Conclusion: Functional results were marginally in favor of CAS. CAS was more predictable than CONV when aiming for mechanical alignment of the prosthesis. Operation time was longer with CAS. The results were limited to one navigation system and one prosthesis brand. Long term effect must be further investigated.

5. General discussion

5.1 Methodological considerations

5.1.1 Study designs

The computer navigation project

There are strict regulations for the release of new kinds of medications to the market, and most industrial countries apply to these regulations. Paradoxically, the same strict regulations are not present in the regulation of new medical technologies. However, the medical community and health care providers are eventually getting more concerned about the quality and cost-effectiveness of new technologies as the health care costs seem to have an infinite growth [66]. This thesis is part of a project investigating the need and value of computer navigation in total knee replacement surgery (CAS), financially supported by the Norwegian Research Council (project no.191051). The computer navigation technology is costly and time consuming, and there has not been sufficient evidence to justify a large scale use of this technology. Still however, the technology has been widely used in Europe, Australia, Asia and North-America.

In order to evaluate the effect and usefulness of CAS, our first challenge was to select appropriate parameters and study designs. The concerns about increased costs with CAS initially urged us to perform a cost-effectiveness analysis (CEA) to outline what improvements were required for CAS to be cost-effective, with respect to survivorship and quality of life. Secondly, we performed an observational register study, analyzing CAS in the Norwegian Arthroplasty Register. The register study evaluated short term complications and survivorship with and without CAS, and revealed some weaknesses with particular implants prompting further investigations in a second register study of various prosthesis brands and designs, with respect to survivorship and revision causes. Finally, a randomized controlled trial was

performed comparing CAS to CONV. Functional and radiological outcomes were evaluated and complications reported.

Cost-effectiveness analysis (CEA), the Markov model

A cost-effectiveness analysis involves a decision making process. A Markov model was used, as this kind of model is particularly useful in decision problems with risk over time, where timing is important and where the risk varies. The uncertain events are revision and death, and these events are modeled as transitions states. Probability of transition from one health state to another is entered into the model (well with primary TKR, well with revision TKR, dead), and each health state is associated with a certain cost, life expectancy and quality adjusted life expectancy (utility). For the evaluation of events occurring only once in a lifetime, one-year cycles are recommended. We chose an observation period of 20 years (20 cycles), and the costs, expected life years and QALYs for each of these cycles are summed for each of the two treatment strategies. For this study the important question was when (at what improved survivorship level) the potential improvement with CAS was worth the investments, relative to the threshold value. In other words, one is looking at CAS separately, as the evaluated technology. The TKR is common for the two cohorts, so the interesting difference under evaluation is the use of CAS. TKR with and without CAS are both likely to be cost-effective (under the threshold), but when evaluating the gain of CAS, separate from the gain of TKR, the potentially added value of CAS has to be cost-effective in itself. In this respect, CAS is evaluated as an added tool which has to earn its own place in TKR surgery.

CAS in the Norwegian Arthroplasty Register

When the cost-effectiveness analysis had given us an idea of what was hypothetically required of CAS, our next project was to investigate the *in vivo* survivorship of computer navigated TKR. The Norwegian Arthroplasty Register has registered the use of CAS since the year 2005. At the time data from 2005-2008 were available for evaluation. Only short term results could be extracted from this study, so the study clearly had limitations concerning prediction of survivorship. In this study, however,

many aseptic loosenings of the tibial component appeared surprisingly early (table 4, paper II). The reason for that was not found.

Statistical considerations – Register studies vs Randomized clinical trials

Register studies are normally not suited for finding the exact mechanisms behind failures. On the other hand, they are well suited for detection of weaknesses of implants regarding designs, changes of tools, bone cements and other aspects affecting surgical outcome. A register study refers to the results of many surgeons and hospitals, with different traditions, experience and skills. As a result, the study has good external validity, informing us what to expect from an "average" surgeon in Norway. Although the numbers of patients were low for a register study, it had high numbers of patients compared to any RCT in this field. Small differences and rare incidents could be discovered due to a high statistical power. Implant survivorship is obviously an important measure, but ultimately the quality of life of the patient is the most important measure which all other parameters come down to. TKR is about improving the quality of life for the patient. Functional scores may indirectly measure quality of life. Improvements in function may lead to improvements of life quality (unless other aspects in life affect the quality of life in a negative way). Implant survivorship may not always reflect the patient's quality of life, since many patients have severe problems and non-functional knees without getting a revision, due to contraindications to revision surgery (serious co-morbidity, low demand patients, severe psychiatric illness, anxiety etc. [67;68]). Thus, a register study does not tell us the whole truth about our patients. A randomized controlled trial was performed to find out more about these patients, their function in daily living, clinically measured function, pain and quality of life (Paper IV). Additionally, an RCT would verify whether CAS improved alignment, and the RSA part of the trial might predict the impact of CAS on long term survivorship. A disadvantage with most register studies is that the populations and the groups compared are different and adjustments for confounders are needed. Even with adjustments this weakness cannot be fully compensated, due to unknown confounding factors. An RCT is superior to register studies with regard to these aspects, but the numbers of patients in RCTs are often too

small to reveal important differences in the occurrence of rare events, such as infection, reoperations and death. In register studies a minor difference in implant survivorship might not be regarded as clinically important, dependent on follow-up time. In the same way, a difference on a KOOS subscale of less than 10 units is probably not clinically important or noticeable by the patient. The minor differences detected in our RCT may not, in this respect, be clinically important. However, they all had a trend towards better results with CAS. The difference for each individual patient might not be noticeable, but the combination of minor improvements in function and alignment might be clinically important over time. To evaluate the long-term results, a radiostereometric (RSA) study was incorporated into the RCT for the first 60 patients (the RSA study is not a part of the present thesis), and follow-ups on functional outcome will be performed after 5 and 10 years. A multi-center study, with multiple surgeons involved, may be weakened by differences regarding surgical procedures, unequal experience and skills, selection of patients suitable for surgery, a large number of clinical evaluators, different rehabilitation programs and different evaluating tools/procedures (subtypes of CT scanners, radiographs and goniometers). These limitations are known to multi-center studies and clinical trials, and thorough preparations were done prior to the study in order to balance the differences. Surgical procedure, rehabilitation program, clinical and radiological evaluation followed an identical protocol at all participating centers, and all surgeons and radiologists involved in the trial met for discussions prior to the inclusion of patients. The trial involved only one type of computer navigation systems, performed on one type of knee implant. Other navigation systems and other implants may have different results.

5.1.2. Outcome measures

Rationale and explanations to the outcome of a CEA

The CEA was performed from the view of a health care provider, which means that not all costs and consequences are considered, only those pertaining to the health care provider. A CEA is different from a cost-benefit analysis. In a cost-benefit analysis the health gain is given a specific monetary value, and the least expensive alternative is chosen. Monetary value on health effects is problematic and often raises ethical questions. Consequently, most health care analysts prefer to use a CEA. In a CEA the two alternatives (in our case CAS vs CONV) have different costs, and both affect health. The alternative with the best cost per health gain ratio is preferable. Various alternatives are ranked according to this ratio and there is a threshold (cut-off) for how much the decision maker is willing to pay for the health gain[69]. When/if this threshold is reached, the alternative is no longer an option. We particularly wanted to evaluate the impact of age and patient volume on cost-effectiveness. The cost-effectiveness analysis performed compared CAS and CONV. The health gain (effectiveness) was measured by improvement of Quality Adjusted Life Years (QALYs). The cost-effectiveness measure was then the ratio of increased costs per QALYs saved (the incremental cost-effectiveness ratio (ICER). Cost-utility analysis is often used as a synonym for CEA[70]. The utility value can be assessed either by a rating scale, standard gamble or time trade off, and the improvement of the utility value is the health gain measured. In addition, there are health indexes like EQ-5D (EuroQol) and the Health Utilities Index (HUI) where a utility value is derived from the patient's answers to a health state questionnaire weighed against a reference population. The utility values chosen for our analysis were similar to the values of large randomized trials and the Swedish Arthroplasty Register, based on EQ-5D [56;57]. The difference between utility values before and after surgery represented the health gain. This health gain was assumed equal for CAS and CONV in the model. A hypothetical improvement of survivorship with CAS would result in fewer revisions and a smaller loss of utility. A direct comparison was possible since the utility values

for both methods were set equal, and the revision procedure and consequently the loss of QALYs associated with this procedure, was equal for both methods. The impact of the revision rate on the cost-effectiveness was the important factor to evaluate. If the health gain by avoiding a revision operation had been set to a smaller value, the likelihood of cost-effectiveness for CAS would consequently have been lower, given a positive effect of CAS on survivorship.

A hypothetical CEA model

The set-up of this hypothetical model must be comprehended as different from a model with known effects of CAS. In this model a hypothetical effect of CAS was entered into the model and adjusted up and down to find the required levels of effect needed to achieve cost-effectiveness. The effect might be small or large. A large effect would have a high likelihood of achieving cost-effectiveness, and a small effect would have a lower likelihood of achieving cost-effectiveness. The cost-effectiveness was also dependent on the patient volume, since the costs were shared and would be lower per patient with a large volume. Furthermore, we wanted to check if the cost-effectiveness was dependent on the age of the patient. Life expectancy, risk of revision, cost of revision, and cost of CAS all affect the incremental cost-effectiveness ratio (ICER).

Limitations to the CEA model

For simplicity, no re-revisions were entered into the model. We know that the risk of re-revision is higher than for the first revision, and according to the annual report 2012 from the National Joint Replacement Registry in Australia, the cumulative percentage of re-revision of knee replacements is 23.5 (21.4-25.7) after 10 years. The numbers of re-revisions are low, especially for the older patients, but inclusion of re-revision data might have altered the results for the younger cohort. In a definite evaluation of CAS with known effects on survivorship, this parameter should probably be included in the analysis, but for our theoretical approach, the inclusion of only one revision was regarded sufficient. The functional outcome and eventual

complications were regarded similar with or without CAS, in this model. We know from our RCT (paper IV) and other trials[71] that this is not far from the truth, and the approximation is not likely to have distorted the results of the CEA. Longer operation time with CAS did not generate extra costs in our model, because some authors argue that by increasing experience the operation time will decrease and perhaps be shorter than with a conventional technique. Also, the exploitation of the time saved by CONV is dependent on the local organization.

Limitations to the CAS registry study

A longer operation time was indeed found in our register study of CAS. But as mentioned above, the consequences of the time prolongation are uncertain. Various CAS systems and software might differ with respect to time consumption. Also implant brands differ, so the results could be influenced by the systems or brands used by single hospitals or single surgeons. The Kaplan Meier analysis of implant survivorship showed inferior results with CAS. The Cox regression analysis of implant survivorship, adjusted for age, sex, ASA category, method of fixation, prosthesis brand, diagnosis and previous knee surgery, confirmed the inferior results with CAS, but there might be other confounders with respect to hospital differences. However, there were 64 hospitals in the study, and only 20 of them used CAS, so adjustment for hospital was regarded unsuitable. Additional adjustment for operation time did not alter the results. On the other hand, a longer operation time involves longer exposure to surrounding bacteria, and a risk of a low grade infection, subsequently leading to loosening, increases. It is possible that this effect is not captured by the present study or by the reporting surgeons. The mechanisms of loosening are probably multi-factorial, involving polyethylene wear and biological response, shear forces (alignment, ligament balancing, patellar tracking, roll-back, rotation, edge loading), low grade infection, bonding between cement and implant, cementation technique and inherent qualities of the materials used in the manufacturing process. Consequently, the exact mechanism of the loosening process might be difficult to reveal, but the sum of the effects of CAS can be measured.

Furthermore, a learning curve might negatively affect the outcome and was investigated by eliminating the first 20 operations, but the results were the same. However, the elimination of the first 20 operations at each hospital does not guarantee that the early operations of each surgeon were eliminated. There still might be a substantial number of “learning curve” patients in the remaining data. The data involved both cemented, uncemented and hybrid TKRs. The method of fixation was adjusted for in the Cox regression analysis, but the adjustment is not always good enough to rule out the possibility of confounding. To strengthen our analysis, a subanalysis with cemented implants only was done. The inferior short term survivorship with CAS was still statistically significant, thus verifying our previous findings. For the uncemented and hybrid knees the number of patients was too low to conclude, but the trends were towards inferiority with CAS.

Relevance of an implant brand/design study

As we revealed a weakness for computer navigated LCS Complete in paper II, we decided to look deeper into the problem with aseptic loosening of the tibia, suspecting the weakness might be due to the implant specific features and design, or the principle of mobile bearing. Paper III is a register study addressing these issues in 7 different implant brands, with three different designs; fixed modular bearing, fixed non-modular bearing (also called mono-block) and mobile bearing. Strictly speaking, this issue is not directly related to CAS, but the problem seemed to be enhanced by CAS. Thus, this article fits nicely into this thesis analyzing the effect of CAS in TKR. Paper III had the same limitations as paper II concerning causes and mechanisms behind failures, but the number was higher and the power increased. The LCS Complete was one of the most frequently used implants in Norway at the time, and it was supposed to have equal or improved results compared to the LCS Classic which in Norway was replaced by the LCS Complete from the year 2007. If LCS Complete and Classic were to be regarded as one implant brand, it would be the most frequently used implant since the registering started in 1994. The second most used implant brand was the Profix knee, and it was natural to choose this implant brand as the

reference brand in the study, for comparison. The Profix and the LCS were of different designs, and we wanted to widen the scope of the study also to include the mono-block design, in order to prepare for an evaluation of the three design categories as a secondary outcome. The computer navigated implants were excluded from the study to distinguish the impact of CAS from the impact of implant specific features and design. Only TKRs without patella resurfacing were included, as only 2.2% of TKRs reported to the NAR were implanted with patella resurfacing in the year 2009. For all TKRs reported since 1994, 8.8% have been implanted with patella resurfacing [72].

Limitations to the implant brand/design study

Patella resurfacing as a secondary procedure in patients with persistent pain, is regarded a revision operation in the NAR. The patients who experience pain will often receive a patella resurfacing and will then be excluded from further evaluation in this trial. Theoretically, some of these “pain” patients might have an aseptic loosening as the cause of their pain, and might subsequently go on to another revision operation without being captured in this study. This weakness was not discussed in paper III, but this aspect was pointed out after publication. Therefore, a subsequent analysis was performed firstly by excluding patients who received a secondary patella resurfacing as a type of revision, secondly by excluding patella resurfacing performed in patients with pain as the only reason for revision. However, the results were not altered. As already pointed out, a register study cannot clarify the mechanisms behind failures, but as shown in paper III, the causes of revision might reveal weaknesses prompting further investigations. As a consequence of these findings, a new study was initiated to investigate the LCS implants in a laboratory setting (not a part of the present thesis). Orthopedic surgeons in Norway were asked to deliver revised LCS implants for analysis in the BioMat Lab at Haukeland University Hospital. Also, unused implants were requested for geometrical analysis and roughness measures.

Sample size and strength of the RCT

To overcome the weaknesses of register studies with different populations, surgeons, traditions, implants, technologies, infrastructure, rehabilitation programs, reporting issues and adjustments, an RCT was performed comparing CAS vs CONV. Representatives from the four participating hospitals met to agree on a common protocol to equalize the treatment and clinical set-up (Appendix 2). Power calculations estimated 64 patients in each group for functional outcome differences and 79 patients for radiological differences. Our recruitment exceeded that number with 97/95 patients in each group, but in one hospital there were some patients lost to follow-up due to logistical problems. At one year, 88 patients in the CAS group and 87 patients in the CONV group were evaluated with functional scores, however still with a great margin according to our power calculations. A smaller study would probably not have revealed the differences found in this trial, and a false negative result (type II error) could have been made. The study was not powered to detect differences in complications and revision operations.

RCT scoring systems

We used 4 different scoring systems for the functional evaluation: the EQ-5D, VAS (Visual Analogue Scale), KOOS (Knee injury and osteoarthritis score), and KSS (American Knee Society Score). The first three score systems are patient administered and the last one is clinician administered. For all functional scores the patient was asked to answer the questions according to their experience with the knee under study, but some patients may have been confused by pain and reduced function of the opposite knee. The Charnley category showed that there were a few more patients with bilateral osteoarthritis of the knee in the CAS group, but the difference was not statistically significant, so the laterality confusion should be equal for both groups. The EQ-5D was developed by the international EuroQol group and measures quality of life along 5 dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Each dimension has 3 levels: no problems, some problems, extreme problems. The combination of answers generates a score

which is weighed against a standard population similar to the one studied (www.euroqol.org). A newer version is developed including 5 levels to avoid a ceiling effect, but it is not available in Norwegian. The version used in our RCT may not be suitable for detecting differences among the good and the excellent outcomes, due to this ceiling effect. The VAS scale is a 100 mm long scale rating the worst experienced pain of the investigated knee during the last week, from 0 (no pain) to 10 (the worst pain you can imagine). A weakness was that some patients marked the scale with a cross rather than a line, some crossed outside the line and some did not mark the scale at all. The KOOS score is based on the WOMAC score which is recommended by the JBJS(Am) for studies evaluating TKR[73]. The WOMAC score can be calculated from the KOOS scores. KOOS was developed for knee injuries (anterior cruciate ligament and meniscal) to detect smaller clinical differences. The KSS contains a clinical evaluation and questions asked by the clinician. It is recommended to use this scoring system along with a patient administered scoring system in TKR studies [73].

Measuring blood loss

Bleeding was measured as the drop in hemoglobin levels and was also calculated according to a specific algorithm to find the blood volume loss [74]. The hemoglobin and hematocrit values were tested 2 weeks before surgery and after 3-4 days, before discharge. Thinning of the blood due to intravenous fluid administration was regarded less likely after 3 days, but may have influenced the results. The algorithm used for calculation of blood loss is not a validated research tool, but rather a practical guide for anesthesiologists. The values may not represent the true blood loss, but were used for comparison between the groups and as a supplement to the hemoglobin drop.

Radiological outcome (local adaptions to the Perth protocol)

The radiological measures were based on the Perth protocol [8], and some local adjustments were made. The Perth protocol was not very instructional on how to perform the measurements on the CT scans, so we arranged several meetings with our

radiologists to find consensus for a protocol (Appendix 13). The Imperial protocol was discussed as a more radiation protective protocol, but the tests showed that this protocol was difficult to perform in our local setting, and we were concerned that the images achieved by this protocol would not be of adequate quality for radiological measures. The Perth protocol was still radiation protective, and for the age group involved in the RCT, the risk was negligible. The protocol was approved by the regional ethics committee. The evaluation of the CT scans and long length radiographs were initially performed by radiologists, but this was more time consuming than expected. We then educated two research assistants (one nurse and one medical student) to perform the measurements. The software (IMPAX Agfa version 6.4.0.4551) and monitors (LCD 24'' widescreen, 16:10 aspect ratio) used for the measurements had to be of high resolution (1920x1200 pixels). The evaluator must enlarge the images and choose the appropriate tools and algorithm to get accurate measurements. Short-cuts were possible and might have compromised the accuracy of the measurements. For future studies, an automatization of the measuring procedure would probably improve the repeatability and accuracy of the protocol.

Blinding

The blinding procedure of the radiological evaluator was not successful, as the pin holes could be seen on both the CT scans and the full length radiographs. This is of course a weakness, but the radiological assessors were not directly involved with the patients, so the blinding procedure was not further compromised. "Sham" incisions were part of the blinding procedure. The pins fixed to the femur could be placed within the main incision, but the pins for the tibia were less practical to situate inside the incision, so they were placed distal to the main incision through two minor stab incisions. All patients received these stab incisions, even if they got a conventional TKR, for the purpose of blinding. In this way the physical therapists evaluating the clinical outcome were blinded as well. The CAS equipment was always switched on during the operation, regardless of method used, and the patient's head and sight was behind a curtain. We believe the blinding procedure was adequate, although the most

scientifically optimal blinding procedure would have involved the surgeon, which was not practically achievable. Future studies might consider blinding the radiological evaluators by placing a blinding strap in the area of the pin sites when performing CT scans.

5.2. Results

5.2.1 Cost-effectiveness, ICER

The threshold

The cut-off value of NKr.500.000 per QALY is a large sum of money, and it is not given that any new technology or medical invention with a lower cost would be approved for clinical use. On the contrary, this is the upper threshold for what is acceptable if the technology is regarded as useful and needed, evaluated against other alternatives. A TKR is cost-effective with or without CAS. However, the TKR is not the object investigated for cost-effectiveness. CAS is the object in itself. So the interesting feature is what CAS adds to the health of the patient, relative to the elevated costs. At first, we evaluated which method was the most cost-effective of the two, and what effect on survivorship was required by CAS, to be superior to CONV. Furthermore, what improvement was needed with CAS for this improvement to be cost-effective, relative to the threshold?

Patient volume, age, incremental costs

In order to get below the healthcare sector's threshold value for cost added per QALY gained, the probability of revision needed to be reduced by somewhere between 0.8% and 13.0%, depending on patient volume and the cost of the computer navigation equipment. It was clear that patient volume, not surprisingly, impacted significantly on the cost effectiveness of computer navigation. At high patient volumes the improvement required was less than at low patient volumes. Age appeared not to influence the probability of getting below the threshold value to any great extent. The reduction in revision costs relative to health gain was important when evaluating the impact of age. A reduction in revision costs and health gain was preferable in both age groups. The ICER (incremental cost effectiveness ration) is the ratio of added costs per added QALYs. Since this is a ratio, the size of the numerator and denominator is important. Health gain intuitively seemed likely to be more substantial in the young cohort because of a longer life expectancy. On the other

hand, the revision costs were lower in the old cohort, as a result of lower revision rates. The superior health gain of the young cohort, compared to the old cohort, did not seem to outweigh the higher costs of revisions in the young cohort. In order to get below the threshold of the sector's willingness to pay, the probability of revision would have to fall by at least 7.5% (of 10.2%) for cohort 1(age 60) at a volume of 25 knee replacements per year, and by at least 1% at a volume of 250 knee replacements per year. For cohort 2 (age 75), the probability of revision needed to fall by at least 7% (of 4.9%) at a volume of 25 prostheses per year, and by at least 1% at a volume of 250 prostheses per year.

Survivorship vs revision rates in the CEA

We converted this information from impact on revision rates to impact on survivorship and found that the improvement needed was an increase in the 10-year implant survivorship in cohort 1 from 89.8% to 90.6% at a volume of 25 prostheses per year, and from 89.8% to 89.9% at 250 prostheses per year. In cohort 2, implant survivorship needed to improve from 95.1% to 95.4% at a volume of 25 prostheses per year, and from 95.10% to 95.14% at a volume of 250 prostheses per year (fig. 4, paper I). We made this conversion to make the numbers more consistent with the numbers from the NAR which presents Kaplan Meier survivorship data rather than cumulative revision rates. This conversion is only valid if we assume a linear relationship between time and risk of revision. This assumption is not quite correct as we know that the risk of revision varies over time, but the error has marginal impact on the results, and is just an approximation to make the results easier to understand for readers more familiar with survival rates. Doubling the cost had little impact on the probability of getting below the threshold value of NOK 500,000 at high patient volumes. For low patient volumes, doubling the cost would require further improvement of implant survivorship (for cohort 1: from 90.6% to 91.1% and for cohort 2: from 95.4% to 95.7%), to get below the healthcare sector's threshold value of NOK 500,000 per quality-adjusted life year. We concluded that the healthcare sector may be willing to pay for the added cost of CAS provided the patient volume

was large, the price of CAS did not rise, and there was positive impact on implant survivorship. The probability of getting below the financial threshold for added cost per quality-adjusted life year (gained) was falling at rate with falling patient volumes and falling survival rates. For most hospitals in Norway, the patient volume was lower than 250 per year, and there was no evidence showing a positive impact on implant survivorship at that time. Based on this analysis we suggested a deferral of investments until such data were provided.

5.2.2 Implant survivorship, complications and revision causes

Short term survivorship with CAS

To explore the effect of CAS on implant survivorship, we performed a register study based on data from the Norwegian Arthroplasty Register (paper II). We found that computer navigated total knee replacements had a lower 2 years survivorship than conventionally operated knees. In contradiction with the expected improvement of survivorship, the results deteriorated with CAS. The inferior short term survivorship of CAS compared to CONV was somewhat surprising taking into account the optimism regarding the effect of CAS on survivorship. Improved alignment by CAS was thought to give better survivorship by improved resistance to the wear, shear and stress forces leading to aseptic loosening. However, wear is expected to occur later in the "life of an implant", leading to osteolysis and aseptic loosening. Thus, one theory was that there was more edge loading with a mobile bearing design and that the tibial component was wobbled loose. Another explanation might be that a low grade infection is hard to diagnose and could have been missed when reporting to the register. Particularly the LCS Complete showed inferior results, and when comparing the two hospitals with the highest volume of LCS Complete, there was a tendency that one hospital was inferior (RR=2.5, p=0.168, not published), however the numbers were too small to conclude. The reason for this possible hospital specific inferiority could be due to a large number of surgeons and low volume per surgeon, insufficient education before starting with CAS, insufficient surgical skills, cementing technique or experience. Other possible explanations are mentioned in paper II. There was no evidence of an increased risk of fracture with the use of computer navigation. However, fractures not leading to removal of the implant, or parts of an implant, are not reported to the register unless they occur as an intraoperative complication. The analysis of revision causes showed a trend towards more deep infections and aseptic loosening with CAS, and if true, the longer operation time is one of the factors of concern. On the other hand, the analysis of revisions due to malalignment and instability trended towards better results with

CAS, compliant with the expectations from the CAS technology. These trends are weak and not emphasized in the article due to lack of statistical significance and a low number of revisions (table 4, paper II).

LCS Complete inferior, with and without CAS

So far, we knew that computer navigated LCS Complete had inferior survivorship compared to conventionally operated LCS Complete. In addition, we saw that even when conventionally operated, this implant seemed to have an inferior survival curve in the Cox regression analysis, compared to other implants. Especially, the early drop of the survival curve the first few months was of concern. However, the number of revisions among LCS Complete knees in this study was too small to conclude on causes of revision, and the inferiority of the survival curve was not convincing for the conventionally operated LCS Complete. The increased risk of revision for computer navigated LCS Complete, could be an effect of inferior compatibility between computer system and implant brand, and we discussed whether mobile bearing TKR was more difficult to navigate, particularly with an open navigation system. We decided to further investigate the revision causes of TKRs, and of the mobile bearing LCS Complete in particular, in another register study. Also, the National Joint Replacement Registry of Australia and the Southern California Permanente Medical Group, both had found that fixed bearings had a lower risk of revision compared to mobile bearings [45;75]. In a 10-12 years follow-up of a randomized controlled RSA study, there was no evidence of superior fixation with an AP-sliding, rotating mobile bearing design compared to a fixed bearing [76]. However, the AP-sliding bearing is different from the rotating platform bearing of the LCS Complete. In the Australian register the 10 years cumulative percent revision of the LCS Complete was marginally inferior to the fixed bearing Profix knee (5.4 vs 4.8). That leads us to paper III.

Survivorship and revision causes in TKR

We evaluated the rates of survival and cause of revision of the seven most used implant brands of cemented primary total knee replacement (TKR) in the Norwegian Arthroplasty Register during the years 1994 to 2009 (paper III). We found that, the LCS Complete had a 7-fold increased risk of revision due to aseptic tibial loosening, compared to the Profix knee. Similarly, the LCS Classic had an increased risk, not only for tibial loosening, but also for femoral loosening. These findings suggested that aseptic loosening was related to the mobile bearing design of these implants. However, the LCS Complete and Classic tibial components used in Norway had a cone shaped stem called "non-keeled", and in addition the Complete had cement pockets on the undersurface. The undersurface of these tibial components was "smooth". The LCS knees used in Australia were mainly "keeled" stems. These design features could both have led to reduced rotational stability and will be further investigated by our biomaterial research group. However, we found an increased risk of aseptic loosening in the Duracon knee and the AGC Universal, which could not be explained by the design. The NexGen and AGC Anatomic knees are of the same design principles, but the results are superior to Duracon and AGC Universal. Other explanations were sought. The Duracon knee had excellent results in the Australian Arthroplasty Register, so there had to be some factor linked to the Norwegian surgeons, which could explain the results. In the year 2005 the Duracon TKR was introduced in one geographical region of Norway as a result of a tender process, and therefore the local surgeons were obliged to go through a learning process. The learning curve, or the compulsory change of implant, seems to have had a negative impact on the results [77]. For the AGC Universal, there is no left/right femoral component, and it is not supposed to be as patella friendly as the AGC Anatomic. The higher risk of revision due to aseptic loosening of the tibial component is not easy to explain, but might be related to increased shear and wear forces with the "universal" femoral component. Consequently, the inferior results of computer navigated LCS Complete found in paper II might have been worsened by the fact that this implant had a high risk of aseptic loosening, regardless of the use of computer navigation. However, the risk of aseptic loosening does not explain why computer navigated LCS Complete was inferior to conventionally operated LCS Complete. Computer

navigation of this implant seems to be a bad idea. First of all, the implant was prone to loosening. Secondly, the implant may not be easy to navigate with an open navigation system. CAS might enhance the mechanisms leading to aseptic loosening of the LCS Complete. Thus, the combination of these weaknesses might explain our finding in paper II; inferior results for the computer navigated LCS Complete compared to conventionally operated LCS Complete.

The survivorship of the computer navigated Profix knees were not found to be inferior to conventionally operated Profix knees in paper II. The RCT in Paper IV is only investigating the impact of CAS on Profix, and the results of the RCT might have been different with other implants.

5.2.3 Functional outcome, complications/bleeding, operation time

Functional outcome

In our study (paper IV) we found small differences, and some changed from statistically significant at 3 months to non-significant at 1-year. Only subscales of KOOS were different for the groups. EQ-5D, VAS and KSS (function and knee score, including ROM) were similar in the two groups at 3 months and 1 year follow-ups. There is a risk of over-emphasizing the importance of statistically significant findings, thus making a type I error (false positive results), especially since the RCT was planned and powered to reveal larger differences, i.e. clinically important differences. The risk of making a type I error increases with a large number of parameters. The clinical significance of this marginal improvement is uncertain.

Complications, bleeding

There were no more complications with CAS, but some new complications like fracture at the site of the fixator pins, and technical failure prolonging the operation time as the surgeon had to switch to conventional technology are of concern, and may lead surgeons away from CAS, as the positive effects are marginal this far. The trial reminded us that TKR is not a procedure without risks. Lung emboli could be a life threatening complication, and infection is probably one of the most feared

complications, as the infection can be difficult to treat, which in turn might lead to amputation, as in one of our patients. The prolongation of operation time with CAS might lead to an increased risk of infection [78]. To verify such risk, a large number of patients is needed, and a register study is more suitable for that purpose. Calculations performed by our colleague Håvard Dale in his thesis for PhD, showed that a total of 18000 patients are needed to detect a 50% increase in infection rate after hip replacement [79]. Similar numbers would be needed for knee replacements.

Bleeding was similar with the two methods. Some have advocated that CAS reduces bleeding while avoiding intramedullary violation [14], but this effect was absent in our RCT. One of the reasons might be that all patients received tranexamic acid, thereby minimizing the risk of bleeding from the intramedullary canal.

Operation time

Operation time was 20 minutes longer with CAS. In Paper I we found 15 minutes longer operation time with CAS. Both studies confirm the assumption that CAS is time consuming. For some centers the prolongation may imply fewer operations per day, dependent on how the unit is organized. However, some surgeons claim that the operation time is prolonged in the beginning, but decreases with increasing experience. Like all procedures, the operation time will decrease as the operation team gets more experience with the procedure, and with improvements of software and hardware, it is probably reasonable to assume that the operation time will be reduced. Various CAS systems may vary with regard to time consumption.

5.2.4 Alignment, intra-/interobserver correlation

Coronal (frontal) alignment

Alignment of the tibial component was superior for the CAS group with respect to outliers. Also, for the sum of the tibial and femoral components (alignment of the limb) there were fewer outliers with CAS. Not always was the alignment of the limb good when the alignment of the tibial component was good. A patient could have a

perfectly aligned tibial component and a malaligned femoral component leading to an overall malalignment of the limb. CAS might guide the surgeon not to enhance a malalignment of the limb when one component is badly positioned and the next component is about to be implanted. The malalignment of one component (femoral or tibial) might be corrected or neutralized by the other component (femoral or tibial). If a component is in varus, the other one could be placed in valgus. The effect or hazards of creating an oblique joint line rather than a perpendicular joint line, with reference to the mechanical axis, is not known. Theoretically however, shear and wear forces would increase. This corrective procedure might also be possible to perform without CAS, and to what extent CAS is better or worse than CONV in this regard, is not evident. Also the cementing procedure may alter the position of the components by converting varus into valgus just by adding more cement medially or laterally. We were not able to evaluate this effect on our radiological images as the bone cuts were often not visible. The measured radiological effect of CAS might have been weakened by the use of cement, if the cementing procedure distorted the alignment.

Sagittal alignment

Furthermore, the tibial slope was closer to the target with CAS, with fewer outliers. One might expect improved ROM in the CAS group due to a better tibial slope, but this effect was not found in our study. The femoral component was placed in a slight flexion on average. Flexing the femoral component of a Profix knee, results in a larger anterior posterior offset. The surgeon might choose to flex the femoral component as an alternative to going up one size, when facing the problem that the correct size seems to be in between two implant sizes. This technique is easier with CAS, and the expected sagittal femoral alignment with CAS was thought to be in more flexion. On the other hand, CAS is prone to leave the femoral component in more extension due to the difference between anatomical and mechanical axes in the sagittal plane. The anatomical axis seems to be more in flexion than the mechanical axis, thus it is recommended to flex the femoral component 6 degrees with CAS to

compensate for this difference [80]. This counter-effect and varying knowledge about these aspects might have affected the alignment in both directions, leaving the groups with no statistically significant difference.

Rotational alignment (positioning)

The rotational positioning was similar in the two groups with respect to outliers and mean angle measurements. The large proportion of mismatch outliers, 34.7% and 36.5% (CONV and CAS respectively), suggests that neither CAS nor CONV are optimal tools for correct rotational positioning of the implant. Difficulty in defining the antero-posterior plane of the tibia and the transepicondylar axis of the femur has been much debated [81;82], and it does not seem like CAS is the solution to this problem [22]. On the other hand, an improvement in rotational positioning was not expected, since the computer software requires the surgeon to register "Whiteside's line", transepicondylar axis or posterior condyles as anatomical references to the computer (in our study we agreed to use Whiteside's line in all patients). The inaccuracy is not in the software, but in the surgeon's registration of the anatomical landmarks, similar to CONV. Consequently, the similar results in the two groups were not surprising.

Intra- and interobserver correlation

An intra-/interobserver correlation study was carried out, and the results were acceptable (paper IV), defined as absolute agreement for single measures. However, the rotational measurements correlated less than in the frontal and sagittal plane. The reason was that anatomical landmarks were difficult to mark out. Especially the antero-posterior axis (AP-axis) of the tibia and the transepicondylar axis of the femur were difficult to find. Also the tibial component in the frontal plane showed some variation in the measured angle. The center of the ankle was not always easy to define, which might have caused a marginally lower measurement correlation. Consequently, the results concerning rotational alignment of the implant must be interpreted with care. However, the target was to achieve alignment within 3 degrees of valgus or varus, implying that all knees implanted within a range of 6 degrees are

defined as optimal, whereas those outside this range are defined as outliers. Thus, excellent aligned and substantially malaligned knees were likely to be judged correctly, and borderline aligned knees (2-4 degrees outside the target) might have been judged wrongly as well aligned or malaligned, due to inaccuracy of the measuring. These uncertainties were most profound for the rotational alignment (positioning), and are probably less important for the other measurements.

5.3 In view of the literature

CAS vs CONV, aligned vs malaligned

Our trial investigated the relationship between functional results and the use of computer navigation in total knee replacement, as the primary outcome. Secondary outcomes were alignment and positioning of the implant achieved by the two techniques. The functional results of well aligned and malaligned knees must not be confused with the results of computer navigation and conventional technique, and we agree with Harvie et al, that those data should be dealt with separately [83]. There could be reasons other than good alignment, explaining the functional results of navigated knees. Indeed, the computer navigation system allows the surgeon to perform an accurate ligament balancing, and the sizing of implant components might also be different for the two methods.

Well aligned knees can be badly balanced, and malaligned knees can be well balanced, thus alignment might not be the only target. In this trial, however, the target was good alignment, and the principles of ligament balancing taught by Leo Whiteside were applied. However, an extensive ligamentous release might be a difficult procedure, and if not performed correctly, could lead to a badly balanced knee with bad function, even with a perfect alignment. Ligament balancing was performed in both groups, but the extent of ligamentous release could be different in the two groups. The trend towards better functional results in the navigated patients might be a result of less extensive ligamentous release, which in turn could be a result of better alignment. In other words, malalignment of a total knee replacement could possibly lead to an unnecessary ligamentous release. Implant survivorship is probably affected by both ligament balancing and alignment. Thus, the results of a total knee replacement are not only dependent on the tools being used, but probably just as much on the surgical technique and principles. The tibial component position in the sagittal view was aimed at 4 degrees posterior slope, and the polyethylene has a built-in 3 degrees slope, leaving the tibial component surface with a 7 degrees posterior

slope. This target was better achieved with CAS but the effect on range of motion was marginal and non-significant, as opposed to previous reports [84;85].

Is alignment the target?

Several authors have reported improved alignment with CAS [86-89], and a recent meta-analysis of randomized controlled trials concluded that CAS does improve mechanical leg axis and component orientation in total knee replacement [90]. It remains controversial however, whether the improvement of alignment resulting from CAS gives better function [21;91;92] or longevity [93]. In most studies on computer navigation and alignment, the definition of malalignment is based on the early assumptions of Jeffrey et al in 1991, suggesting that good survivorship was related to alignment within 3 degrees of mechanical axis [94]. These assumptions have been questioned by others, and other values have been suggested [95]. However, it seems that the most used definition in trials and among orthopedic surgeons is the definition by Jeffery, but for the sagittal and axial plane, the definitions are not as widely accepted. In lack of clear definitions, we accepted 3 degrees as the limit value of good alignment. Good alignment is probably not the only factor leading to good longevity. Our recent study from the Norwegian Arthroplasty Register reported inferior short term survivorship for certain implant brands when computer navigation was used [96]. However, the Profix knee, used in the present RCT, did not have inferior short term survivorship when computer navigated, in that study. The results of CAS may be affected by the implant and the navigation system being used, as well as surgical training programs and learning curves. In contrast to the short-term results from the Norwegian register study, an RSA study from the University of Leiden showed more subsidence of the tibial component with a conventional technique compared to two types of computer navigation. These results might predict early loosening and inferior survivorship for the conventionally operated knees in the long term [97].

Also, there is an ongoing debate whether perfect alignment is the target in all patients. Some argue that constitutional malalignment may not be fully corrected, and there is no hard evidence to argue against that [98;99]. Choong et al reported that good alignment correlated with good function [100]. They suggested this correlation was due to the use

of CAS, in concordance with the dominating belief that alignment is important for good clinical results and longevity [101-103]. However, concerning functional outcomes, the study did not compare CAS to CONV, but well-aligned against malaligned knees. To our knowledge, no trial has shown a direct correlation between the use of CAS and good functional outcome. A few previous studies have used computer tomography (CT) scans to evaluate the alignment and positioning [21;87;92;104;105]. A CT scan comprises the possibility of detecting both malrotation and malalignment, which might affect clinical function [106].

The alignment of the implant relative to the mechanical axis of the limb is probably more important in the frontal plane than in the sagittal plane. The alignment in the frontal plane is assumed to be important to minimize wear and shear forces, thereby reducing the risk of revision due to aseptic loosening. In the sagittal plane, the forces on the implant work from various angles dependent on the degree of flexion. During gait most knees are designed with a femoral component that has a larger radius of the anterior part of the component to increase the congruency and reduce loading forces on the implant surfaces. In deep flexion, however, a smaller radius is preferable to facilitate flexion of the knee, and most modern TKR implants have a smaller radius of the posterior femoral condyles than of the mid- and anterior part of the femoral component. The focus has been to optimize flexion, roll-back and stability, and to maximize congruency. Consequently, the mechanical alignment in the sagittal plane has not been much debated. In our RCT, the target was defined as alignment of the femoral component with the mechanical axis of the femur, and a 4 degrees slope of the tibial plateau relative to the perpendicular plane of the mechanical axis of the tibia. This 4 degrees slope was shown by Mr. Leo Whiteside to improve range of motion compared to a 0 degrees slope, so we defined 4 degrees slope as the optimal position of the tibial component in the sagittal plane. This position was easier to achieve with CAS than with CONV, but we did not show any benefit of this slope with regard to range of motion, in our trial.

Experienced surgeons and CAS

In a large CT controlled trial by Kim et al, both knees were replaced sequentially under one anesthesia, by one experienced surgeon, using computer navigation in one knee and conventional technique in the other knee [23]. Two different implant designs were used. The navigation system was similar to the one used in our trial. He did not find any difference in outcome regarding alignment or function. Also, he has published mid-term results of survivorship, showing no difference between the two techniques.

Our trial involved 8 surgeons with unequal experience, thus giving a better external validity. When performing sequential operations under the same anesthesia, there might be a transfer of information from the computer navigated knee to the conventionally operated knee, guiding the surgeon. However, this is not the normal situation for most surgeons performing knee replacements. The excellent results by Kim et al might reflect the assumption that great experience with both methods and a sequential operation under the same anesthesia omits the need for a more precise instrument which computer navigation seems to represent. The trial by Chauhan et al. was stopped for ethical reasons when the authors, in an interim analysis, found a better improvement of alignment in the computer navigated group. The 2 year and 5 year functional results have been published later, but the results were similar in the groups [24;83]. However, the numbers were too low to conclude according to our power calculations. Only 60 patients were assessable, 30 in each group. Our power calculations suggested at least 64 patients in each group in order to reveal a difference in KOOS score of clinical relevance (> 10 points on any subscale).

6. Future research

Register study evaluating long term survivorship of CAS vs CONV TKR.

RSA study evaluating long term survivorship of CAS vs CONV TKR.

Laboratory testings and analyses to investigate mechanisms of loosening of the LCS.

Testing of newer/improved types of navigation technology

Long term follow-up of patients in the RCT, 5-year and 10-year survivorship.

Evaluating the benefit of CAS in difficult cases.

Evaluation of the relationship between alignment and functional scores, both in the frontal, sagittal and rotational planes, independent of CAS.

7. Conclusions

1. Cost-effectiveness was first of all dependent on an improvement of long term survivorship, by CAS. However, at high volume centers only a small improvement in survivorship was required. Age did not seem to affect cost-effectiveness. Higher costs decreased the chances of achieving cost-effectiveness.

2. With the introduction of computer navigation to knee replacement surgery in Norway, the short term risk of revision increased for the LCS Complete implant. Even though the difference was small, improved longevity due to CAS might be unlikely for the LCS Complete, considering the inferior short term results. Operation time was increased by 15 minutes. Complications were similar for the two techniques.

3. Risk of revision/Survivorship: Duracon, LCS Classic, LCS Complete and AGC Universal brands had a higher risk of revision (RR 1.3 to 2.6) and a statistically significantly lower survivorship (89.5% to 94.0%) than the Profix TKR (95.3%). The two mobile-bearing implants LCS Complete and LCS Classic were among the brands with a higher risk of aseptic loosening. The assumption that fixed modular-bearing implants are more at risk of aseptic loosening due to polyethylene wear than mobile-bearing designs was not supported by this study. The two mobile bearing implants had a lower revision rate due to pain as the only cause of revision, which might be related to design category.

4. With computer navigation some functional scores were statistically significantly better, but for the patient this effect was marginal and probably sub-clinical in the short term. When aiming at mechanical alignment of the

limb, computer navigation in total knee replacement surgery seemed to be more predictable than conventional total knee replacement.

In summary: With improvements of the technology, and reduced costs, CAS might be a helpful tool to any surgeon. If the short term complications can be avoided by choosing the right implant for navigation, and perhaps also by matching navigation equipment and implant including adequate education of the surgeon, then the long term survivorship might be improved. Further research is required in this field, and until improvements have been made, we suggest deferral of large investments for regular use in primary TKRs.

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9. Papers I-IV (including supplements)

BMC Musculoskeletal Disorders

BioMed Central
The Open Access Publisher

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BMC Musculoskeletal Disorders 2013, **14**:202 doi:10.1186/1471-2474-14-202

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ISSN 1471-2474

Article type Research article

Submission date 7 September 2012

Acceptance date 29 May 2013

Publication date 6 July 2013

Article URL http://www.biomedcentral.com/1471-2474/14/202

An economic model to evaluate cost-effectiveness of computer assisted knee replacement surgery in Norway

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Abstract

Background

The use of Computer Assisted Surgery (CAS) for knee replacements is intended to improve the alignment of knee prostheses in order to reduce the number of revision operations. Is the cost effectiveness of computer assisted surgery influenced by patient volume and age?

Methods

By employing a Markov model, we analysed the cost effectiveness of computer assisted surgery versus conventional arthroplasty with respect to implant survival and operation volume in two theoretical Norwegian age cohorts. We obtained mortality and hospital cost data over a 20-year period from Norwegian registers. We presumed that the cost of an intervention would need to be below NOK 500,000 per QALY (Quality Adjusted Life Year) gained, to be considered cost effective.

Results

The added cost of computer assisted surgery, provided this has no impact on implant survival, is NOK 1037 and NOK 1414 respectively for 60 and 75-year-olds per quality-adjusted life year at a volume of 25 prostheses per year, and NOK 128 and NOK 175 respectively at a volume of 250 prostheses per year. Sensitivity analyses showed that the 10-year implant survival in cohort 1 needs to rise from 89.8% to 90.6% at 25 prostheses per year, and from 89.8 to 89.9% at 250 prostheses per year for computer assisted surgery to be considered cost effective. In cohort 2, the required improvement is a rise from 95.1% to 95.4% at 25 prostheses per year, and from 95.10% to 95.14% at 250 prostheses per year.

Conclusions

The cost of using computer navigation for total knee replacements may be acceptable for 60-year-old as well as 75-year-old patients if the technique increases the implant survival rate just marginally, and the department has a high operation volume. A low volume department might not achieve cost-effectiveness unless computer navigation has a more significant impact on implant survival, thus may defer the investments until such data are available.

Keywords

Artrhroplasty, Computer navigation, Cost-effectiveness, Health economy, Register, Markov

Background

Total knee replacement is considered a cost effective surgical procedure of considerable benefit to the patient. Patients experience a markedly improved quality of life after this type of intervention [1]. On the other hand, there is a risk that aseptic loosening, malalignment and instability, patellar pain or infection, may lead to poorer functionality and quality of life for the patient [2,3]. Over the last decade computer assisted orthopaedic surgery has undergone development, and the use of this type of navigation system is becoming increasingly common (Figure 1). In 2008, 19% of all primary knee replacements in Norway were computer assisted [4]. Better positioning of the prosthesis will in theory reduce the number of revisions [5,6].

Figure 1 Infrared rays are reflected from reflection balls attached to the tibia and femur and back to the camera and the computer. The reciprocal distances and movements measured between the balls are registered by the computer which builds a model of the extremeties axes and anatomy. Surgical instruments are navigated according to the same principle.

A number of randomised studies have demonstrated better positioning of components when computer navigation has been used [7]. The follow-up time for these studies is short, and the results vary when it comes to improved functionality [8]. So far, no-one has been able to demonstrate that computer assisted surgery reduces the number of revision operations. Computer navigation equipment is expensive, and its use prolongs the operation time [7]. Hospitals have scarce resources at their disposal and consequently it is important that the cost effectiveness of new methods and new technology is evaluated, to ensure that every penny is spent on achieving optimal health effects. Within the field of knee replacement surgery good instrumentation is already in use, which is why we need to be extra critical whenever new methods are introduced. History has taught us that new technology and new methods are best introduced in stages, before the market is let loose. This approach provides an opportunity to discover weaknesses at an early stage, to prevent unnecessary harm to patients and the waste of public funds [9]. The Boneloc cement case (used to fix prostheses) which involved 20 Norwegian hospitals from 1991–1993, is but one example demonstrating the importance of thorough evaluation and testing [10]. In theory, computer assisted surgery should result in a better quality of life for the patient, measured in quality-adjusted life years, by reducing the probability of revisions. This model is supposed to guide health care providers in their investments and implementation of new technology. When considering an investment in CAS, it is important to have an idea of what impact this new technology is required to have on patient outcome, in order to achieve cost-efficiency for different age groups and hospital sizes (patient volumes). From the point of view of a healthcare enterprise, we wish to compare the cost per quality-adjusted life year gained by using computer navigation and conventional total knee arthroplasty (TKA) respectively. We also wish to discover how age, patient volume and revision probability influence the cost effectiveness.

Methods

Economic evaluation

The relative profitability of two alternative technologies, computer assisted and convensional surgery, is established using a cost effectiveness analysis. This type of comparison needs to consider possible changes to both benefits and costs. New technology may be cheaper or more expensive, and may have a better or worse impact compared to traditional technology. If computer assisted surgery proves to be cheaper and better, or poorer and more expensive, the solution is trivial, since one technology is dominant. The need for deliberation arises if both costs and benefits change in the same direction. This is normally presented in the form of an incremental cost-effectiveness ratio – ICER, i.e. an equation showing the change in cost relative to the change in effect for the two alternatives. This provides a cost per unit of benefit gained, which in turn may be compared to society's demand for useful employment of resources. In Norway, common practice uses a threshold value of NOK 500,000 for acceptable cost per quality-adjusted life year gained [11]. This does not mean that every intervention that scores below the threshold value should necessarily be accepted. It is also necessary to consider the intervention in relation to the resources available. Consequently, it is important to clarify the perspective of the analysis - patient, healthcare enterprise or society. Our analysis considers the benefits and costs from the point of view of a healthcare enterprise, while more indirect social costs, to relatives for instance, or the cost of absence from work, are excluded.

The measure of benefit is a quality-adjusted life year. This means that consideration is given not only to survival, but also to the quality of the patient's health, measured on a scale from 0 (dead) to 1 (in perfect health), and for how long this health state lasts. There are a number of methods for measuring quality of life. Based on hypothetical questions about what one is willing to sacrifice in order to go from a poor state of health to a perfect state of health, along a number of different dimensions of weakened health, it is possible to arrive at a utility value. The utility values used here have been calculated by means of EQ-5D, a standardised questionnaire (developed by the EuroQol Group) which includes the five dimensions of mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension has three levels – no problems, some problems, extreme problems. By establishing the number of years during which patients experience the different utility values, we arrive at quality-adjusted life years. In turn these can be summarised for a patient population, in order to find the total benefit levels (measure of benefit) to be compared against the costs.

A treatment outcome is often uncertain, and a number of possible states may be envisaged. This means that the costs and benefits included are uncertain values, and we need to take account of the different treatment outcomes by adjusting for this uncertainty. By using a Markov decision model we are able to draw up a useful and clear presentation of different outcomes and their associated probabilities.

Model

A Markov decision model is used to analyse various matters in a number of cycles (20 years in this model). In our model, a cycle equalled one year. We looked at the probability of certain occurences, such as revision and death, within each cycle. Since each occurence had an associated probability, this probability could be used to calculate the relevant costs and utility values within the same cycle (Figure 2).

Figure 2 The Markov Model. The patient undergoes a total knee replacement operation, either by computer assisted surgery (CAS) or conventional total knee arthroplasty (TKA). If the patient survives the operation, he remains in perfect health until he dies of other causes, or needs a revision. The model comprises 20 yearly cycles until all patients have reached the health state of "dead". In each cycle, the patients can either retain the same health state or go to a different health state. The benefits of each surgical method are measured in quality-adjusted life years (QALYs) for each cycle and are summarised after 20 cycles.

Costs and utility values were allocated to each primary procedure and revision procedure. In this model, the patients went from one health state to another at an age-specific frequency and probability based on Norwegian data sources. The theoretical patient cohort accumulated costs and utility values over time. All costs and utility values accumulated over zero time were discounted at 4% per year [12]. The impact of alternative assumptions about the discount rate was tested using sensitivity analyses. Based on the Markov model, we deduced total costs and quality-adjusted life years to evaluate the cost effectiveness of conventional surgical techniques and computer assisted surgery. The model was constructed using a decision analysis software (TreeAge Pro 2009, Williamstown, MA).

The model was based on the following premise: 1) Patients who have their total knee prosthesis implanted by conventional surgery or by computer assisted surgery demonstrate the same post-operative utility value. 2) Mortality after the first year is the same as for other

patients the same age who have not undergone this type of operation. 3) In this model, the patients will need only a single revision operation, and they have utility values allocated for the rest of their lives that match the value normally achieved following a single revision. The values of the various model parameters are given in Table 1.

Cohorts

We have undertaken an analysis of two groups of patients: 60-year-olds and 75-year-olds.

Implant survival

Stipulations were made for implant survival and yearly probability of revision within the two cohorts based on data from the Norwegian Arthroplasty Register for patients over and under the age of 70 who had undergone surgery without computer assistance. For the younger cohort (60-year-olds) the implant survival and probability of revision in the model were set equal to the data for patients under the age of 70, whereas implant survival and probability of revision for the older cohort (75-year-olds) were set equal to the data for patients over 70 years of age (Table 2). For years 1 to 11 we used register data to find the yearly probability of revision by means of the Kaplan-Meier method. For years 12 to 20 we estimated the probability of revision to match the results reported by the Swedish knee arthroplasty register and large-scale cohort studies [13-16]. We have used probability of revision (100% minus implant survival) as a concept in the model, but since Norwegian practice traditionally gives implant survival (100-probability of revision), we calculate the corresponding 10-year implant survival by making an approximation that the probability of revision is the same from year to year (both values are given in Table A in the Additional file 1).

The Norwegian Arthroplasty Register was established in 1987 by the Norwegian Orthopaedic Association; it is publicly funded and is independent of the implant industry [17,18]. The register started collecting data for conventional total knee arthroplasty (TKA) in 1994 [2]. Norwegian surgeons have reported 99% of primary knee prostheses and 97% of revisions [19].

Probability of death

The probability of death within the first year, including perioperative death, was set to 0.63% for cohort 1 and 2.40% for cohort 2, based on linked data from the Norwegian Arthroplasty Register and the National Register for 60 and 75-year-olds. Probability of death after the first year, irrespective of knee replacement surgery, was set equal to the age-specific mortality in the population [20] (Table B in Additional file 1). Studies have shown that the mortality rate is higher for knee replacement revision surgery than for primary knee replacement surgery [21]. The perioperative mortality was therefore set 50% higher for revisions within this model, to 0.95% and 3.60% respectively for cohorts 1 and 2.

Utility values

Patients who receive total knee replacement surgery are expected to enjoy the same quality of life on completion of the postoperative phase and rehabilitation period whether their surgery was conventional or computer assisted. The utility values that were used in the model were based on findings from earlier publications on arthroplasty surgery [22,23]. The pre-operative

value was set to 0.40, the post-operative value to 0.73 (the operation provides an improvement of 0.33). These values are similar to those found in the Swedish hip arthroplasty register, and match the values found for knee replacements [24]. The values are here based on EQ-5D, which is a commonly used instrument for measuring quality of life. Studies have shown that the results following revision replacement surgery is poorer than after primary replacements [3,22]. The value following knee replacement revision surgery was therefore set to an initial value of 0.60.

Disutility value

The disutility value represents the disutility of the reduced quality of life experienced by the patient in connection with a particular health state or clinical outcome [25]. In this model, disutility values represent the reduced quality of life a patient might experience in connection with the operation. The disutility value includes any reduced mobility, increased pain and potential complications that the patient may experience in the perioperative phase. The value is given at the time a patient is undergoing a procedure in the model. The disutility values of conventional knee replacement surgery, computer assisted knee replacement and the revision prosthesis operation, were entered into the model and contributed to a downward adjustment of quality-adjusted life years compared to the patient's total value of quality-adjusted life years. The disutility value of a total knee replacement was set to −0.1 on a discretionary basis and was only allocated to the first post-operative year (i.e. a utility value of 0.73-0.1=0.63 in the model's first cycle). Some have pointed out the risk of increased perioperative morbidity in connection with computer assisted knee replacement operations due to the risk of fracture and infection associated with the positioning of external fixation pins in bone, as well as a longer operation time. However, the incidence of these complications is so low that we allocated the same disutility value to computer navigation as to the conventional technique [26,27]. Revisions, which involve a higher frequency of complications and a longer training period than primary knee replacements, were allocated a value of −0.2 quality-adjusted life years.

Costs

The added cost of computer navigation includes expenditure such as computer hardware and knee replacement software, instruments and maintenance contracts. This was estimated at NOK 1,082,500 per department per year. Disposable equipment (reflection balls) constituted an additional cost, set to NOK 200 per operation. The costs are based on prices obtained from Brainlab Scandinavia, which is a frequently used supplier of computer navigation equipment but supplies no prostheses. The annual cost was calculated based on a five-year usage period for the equipment; the additional cost per department per year was then calculated to NOK 216,500. The cost of disposable equipment was additional. The annual cost was divided by the number of patients operated on at the hospital, in order to find the added cost per operation. Frequent upgrades and new technology may be envisaged to drive the costs up. Consequently, we also looked at the outcome in a scenario where prices were increased by 100%, i.e. to NOK 433,000. The cost per operation, without the use of computer navigation, was based on DRG rate 209A (NOK 146,135) for primary prostheses and 209B (NOK 192,418) for revision prostheses in 2011, which gives the average total cost of these operations at Norwegian hospitals [28]. We expected the hospitalisation periods and staff requirements to be equal with computer navigation and the traditional method.

Analysis

The ICER (”incremental cost-effectiveness ratio”) was found by dividing the difference between total accumulated costs (including the cost of future knee replacement revisions) by the difference in total quality-adjusted life years gained for each of the surgical methods. As in accordance with the guidance provided by the UK National Institute for Clinical Excellence (NICE), our calculations did not include loss of productivity [29]. In other words, our strategy was to find parameter values based on today's literature and data that would produce as true a picture as possible (Table 1). Each cycle (each year) of the model was analysed with respect to accumulated costs and quality-adjusted life years. Finally, the total cost and total number of quality-adjusted life years were analysed for each of the surgical methods (computer navigation and conventional arthroplasty) when all patients included in the model had reached the health state of dead. We used sensitivity analyses to test the stability of the conclusions by varying the parameter values above a certain interval, to see what effect they had on the outcome (ICER). A two-way sensitivity analysis was used for the two age cohorts in order to investigate the relationship between patient volume, the probability of revision, and the cost effectiveness of computer assisted surgery in Norway (Table 24).

Ethics

The Norwegian Arthroplasty Register has permission from the Norwegian Data Inspectorate to collect patient data, based on obtaining written consent from patients (last issued May 24, 2004; reference number 2003/58-3).

Results

In the course of 20 years (20 cycles in the Markov model) a 60-year-old is expected to gain 7.44 quality-adjusted life years, while a 75-year-old would gain 5.46 quality-adjusted life years. The cost of these quality-adjusted life years depends on the patient volume and whether any revision surgery is required. At the outset, we assumed that the probability of revision is identical for conventional atrhroplasty and computer assisted surgery. At a volume of 250 prostheses per year, the cost of conventional arthroplasty in 60-year-olds is NOK 340,606; with computer assisted surgery the cost is NOK 341,558. For 75-year-olds, the cost of conventional arthroplasty is NOK 335,994 while the cost of computer assisted surgery is NOK 336,946. For conventional arthroplasty, this amounts to a cost per quality-adjusted life year of NOK 45,762 for 60-year-olds; for computer assisted surgery, the corresponding figure is NOK 45,890, which is a difference of NOK 128. For 75-year-olds the cost per quality-adjusted life year undergoing conventional arthroplasty is NOK 61,537; for computer assisted surgery, the corresponding figure is NOK 61,712, which is a difference of NOK 175 per quality-adjusted life year. If we make a similar calculation for a volume of 25 prostheses per year, we find that the added cost of computer navigation amounts to NOK 1,037 per quality-adjusted life year for 60-year-olds and NOK 1,414 for 75-year-olds. These values represent a base case before we take account of changes to the probability of revision following the introduction of the new method and how the result is impacted by increased costs.

Figures 3a and b show that when the probabilities of revision are equal, the cost per quality-adjusted life year is higher for computer assisted knee replacement surgery than for conventional knee replacements, and there are no savings to be made. Should the probability

of revision be improved, the number of quality-adjusted life years will increase and therefore reduce the cost per quality-adjusted life year. If the improvement is considerable, savings may be made. Given that the health care sector's maximum threshold value for acceptable added cost (ICER) is NOK 500,000 per quality-adjusted life year gained, we find in both cohorts that a small improvement of implant survival is required to get below the threshold. At low patient volumes and a low impact on the probability of revision, we will risk surpassing the threshold value (Tables C and D in Additional file 1).

Figure 3 The results of the sensitivity analysis for patient volumes in a) cohort 1 (age 60) and b) cohort 2 (age 75). The blue cross-hatched areas show when computer navigation is cost effective. The area between the threshold (black line) and the blue cross-hatched area shows when the cost of computer navigation does not exceed the healthcare sector's willingness to pay per QALY.

In order to get below the threshold of the sector's willingness to pay, the probability of revision will have to fall by at least 7.5% (of 10.2%) for cohort 1 at a volume of 25 knee replacements per year, and by at least 1% at a volume of 250 knee replacements per year. For cohort 2 the probability of revision needs to fall by at least 7% (of 4.9%) at a volume of 25 prostheses per year and by at least 1% at a volume of 250 prostheses per year. If we convert this information, we find that the improvement needs to increase the 10-year implant survival in cohort 1 from 89.8% to 90.6% at a volume of 25 prostheses per year, and from 89.8 to 89.9% at 250 prostheses per year. In cohort 2 implant survival needs to improve from 95.1% to 95.4% at a volume of 25 prostheses per year and from 95.10% to 95.14% at a volume of 250 prostheses per year (Figure 4). The probability of getting below the ICER threshold is virtually the same for the older cohort as for the younger cohort.

Figure 4 The dark blue areas of the columns illustrate the improvement in 10-year Kaplan-Meier implant survival which is required for computer navigation not to exceed the healthcare sector's NOK 500,000 threshold. For example, the column to the far left (25/60 years of age) illustrates this for a hospital with a low patient volume (25 knee replacements per year) and a younger population (age 60).

Doubling the cost had little impact on the probability of getting below the threshold value of NOK 500,000 at high patient volumes. For low patient volumes, doubling the cost would require further improvement of implant survival (for cohort 1: from 90.6% to 91.1% and for cohort 2: from 95.4% to 95.7%), to get below the healthcare sector's threshold value of NOK 500,000 per quality-adjusted life year (Table C in Additional file 1: Figures 5a, 5b, 6a and 6b in Additional file 1).

A sensitivity analysis of variations between 1% and 10% to the discount rate showed no impact on the results.

Discussion

The model suggests that computer navigation may be an alternative to today's conventional total knee replacement, provided there is proven reduction in the probability of revision, and provided the price of navigation equipment does not rise. To date, no studies have documented that computer navigation causes such reduction. In order to get below the healthcare sector's threshold value for cost added per quality-adjusted life year gained, the

probability of revision needs to be reduced by somewhere between 0.8% and 13.0%, depending on patient volume and the cost of the computer navigation equipment. It is clear that patient volume, not surprisingly, impacts significantly on the cost effectiveness of computer navigation. At high patient volumes the improvement required is less than at low patient volumes. Age appears not to influence the probability of getting below the threshold value to any great extent, but there is a minor trend indicating that the probability is greatest in the older cohort, particularly at low patient volumes.

The information provided by this analysis is valuable to hospitals and health politicians focusing on areas that provide as much health as possible for the money. Moreover, the model may be transferred to other high-cost surgical procedures, particularly within areas covered by quality registers that are in a position to provide much valuable information. Ever-increasing healthcare costs make it increasingly important to evaluate the usefulness of new technology. Two of the authors recently published an analysis of the cost effectiveness of computer navigation and knee replacement surgery in the US [30]. They investigated the impact of patient volume on cost effectiveness. It was found that it would be more difficult to achieve cost effectiveness at low patient volumes than at high patient volumes. Norwegian circumstances are significantly different from American circumstances in a number of ways. Our costings are based on prices in the Norwegian market and to the Norwegian Health Service, which are different from those available in the USA. Also, the implant survival used in this analysis is based on figures obtained from the Norwegian Arthroplasty Register.

Strengths and weaknesses

An important strength of this analysis is the use of implant survival data from the Norwegian Arthroplasty Register, which includes prospective data about more than 26,000 total knee replacements [31]. This data strengthens the analysis in that it allows for the probability of revision to be specified year by year, based on results reported by a number of different surgeons at different hospitals in a single country. By combining this data with cost and mortality data from the same country, the analysis becomes relevant at number of levels within the Norwegian Health Service. However, the register holds data only for the last 11 years (at the time of analysis), which meant we had to estimate the implant survival rate for all earlier years.

The model does not take account of the cost of increased operation time. We know that the operation time for bicompartmental knee prostheses in Norway has fallen from an average of 109 minutes in 1994 to 96 minutes in 2008. When using computer navigation, the operation time rose in the period 2005–2008 to 107 minutes in 2008, probably due to a rise in the spread of such navigation equipment combined with limited experience of its use [32]. For beginners, the procedure will be time-consuming, but given experience and technology improvements the operation time is likely to be considerably reduced. Furthermore, the cost of longer operation times will depend on the organisation’s ability to make alternative use of the time saved. The model may therefore over estimate or under estimate the real cost of the procedures.

Utility values are extrapolated in a number of different ways, which means there may be a number of different utility values for a given state [33]. We have looked at values within prosthesis surgery and compared two groups which at first appear identical. However, the values quoted in the literature differ considerably for the same states. There is a risk of over estimating or under estimating the values and this may impact on the result, but because we

limit our analysis to arthroplasty and compare primary operations to revision operations, the consequence of any erroneous estimates will be kept to a minimum.

Another limitation of the analysis is the estimate of probability of changing health states. Data used to determine the yearly probability of revision include patients that had their prosthesis implanted many years ago, without allowing for later developments with respect to technique, material and design. The estimated probabilities may therefore differ from the real values for today's knee replacement patients in Norway, and also may differ between countries. The threshold to perform a revision may be affected by socio-economical state, patient co-morbidities and surgeon's experience, which may differ between countries and regions Furthermore, the analysis does not take account of re-revisions. The probability of re-revisions for reasons of aseptic loosening or prosthesis infection may not be the same in both groups, and this may have impacted on the result of the analysis. The frequency of complications such as thromboembolism, infection and postoperative confusion, may also be different. Furthermore, earlier studies based on Norwegian register data have indicated an increased risk of aseptic loosening and infection with longer operation times [34]. If computer navigation leads to longer operation times, this may impact negatively on the outcomes for this procedure.

We found that high volume centres are more likely to achieve cost-effectiveness. On the other hand, small volume centres might imply that the knee surgeons have a low volume and thereby less experience. Thus, the need of a more precise technology might be greater in a small volume centre. This aspect must be evaluated when considering investments in this new technology.

Further studies, including register studies and randomised studies with long-term follow-ups, are necessary to prove any differences in outcomes between the two surgical techniques. In particular, any impact that computer navigation may have on implant survival will be crucial. It is of considerable concern that there may even be an increased risk of revision in the short term, when computer is being used [32].

Conclusions

The healthcare sector's willingness to pay may be expected to cover the added cost of computer assisted knee replacement surgery provided the patient volume is large and there is positive impact on implant survival. The probability of getting below the financial threshold for added cost per quality-adjusted life year gained, is falling at rate with falling patient volumes and falling survival rates. The patients' age has little impact. The new technique should be carefully tested in a group of hospitals with different age groups and patient volume to evaluate the long term outcome. This model estimates required survival rates to achieve cost-effectiveness with CAS. Until such results are achieved and reported from clinical trials, we suggest deferral of extended investments in computer navigation technology.

Competing interests

Conflicts of interest declared: The project's main sponsor is the Research Council of Norway and Øystein Gøthesen has had a PhD grant.

Authors' contributions

JS and ØG performed the statistical analysis and drafted the manuscript. OF, LH, JEA and HM participated in its design, coordination and interpretation of the results, and helped to draft the manuscript. All authors read and approved the final manuscript.

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Additional file

Additional_file_1 as DOC

Additional file 1 Appendix.

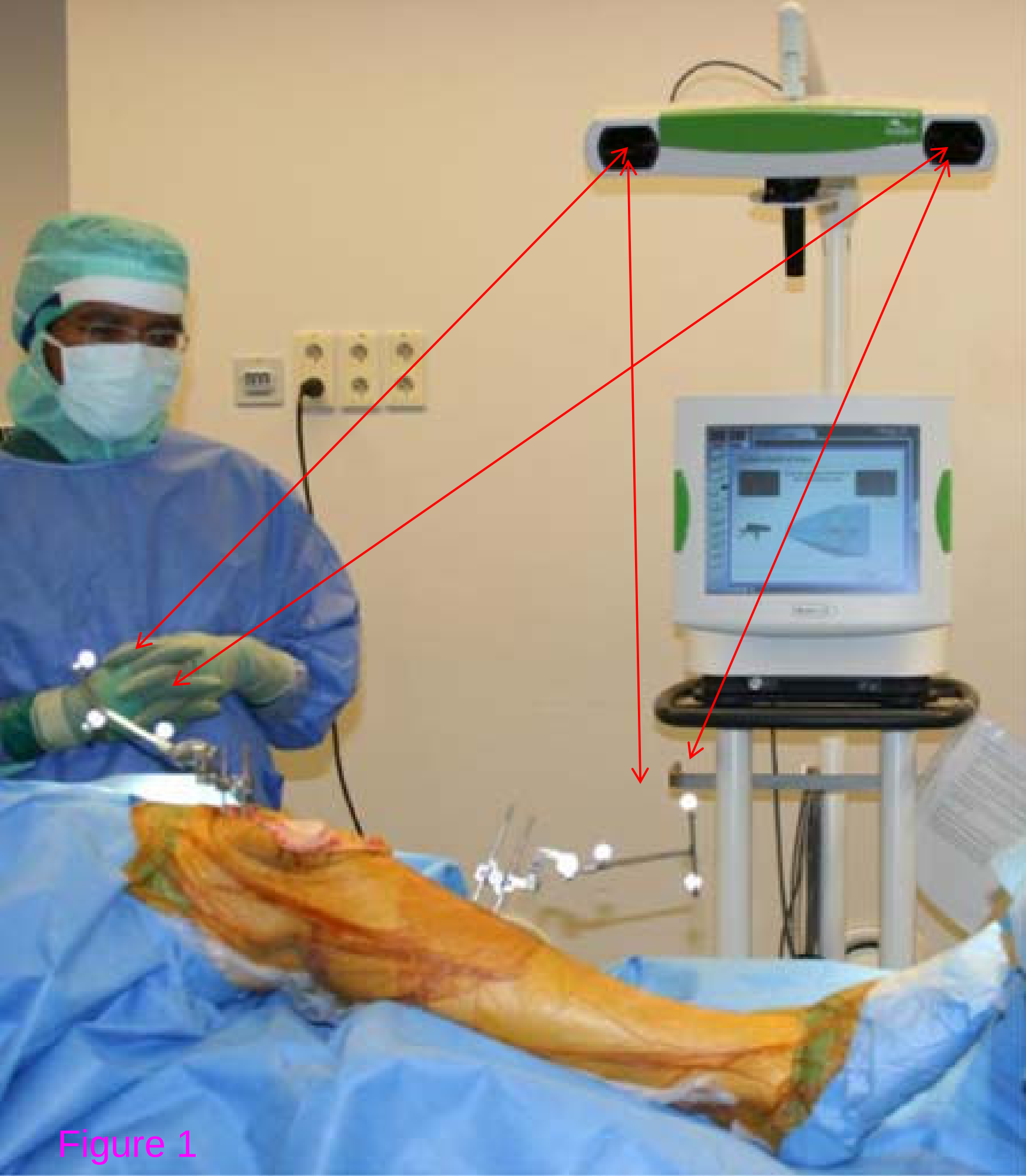


Figure 1

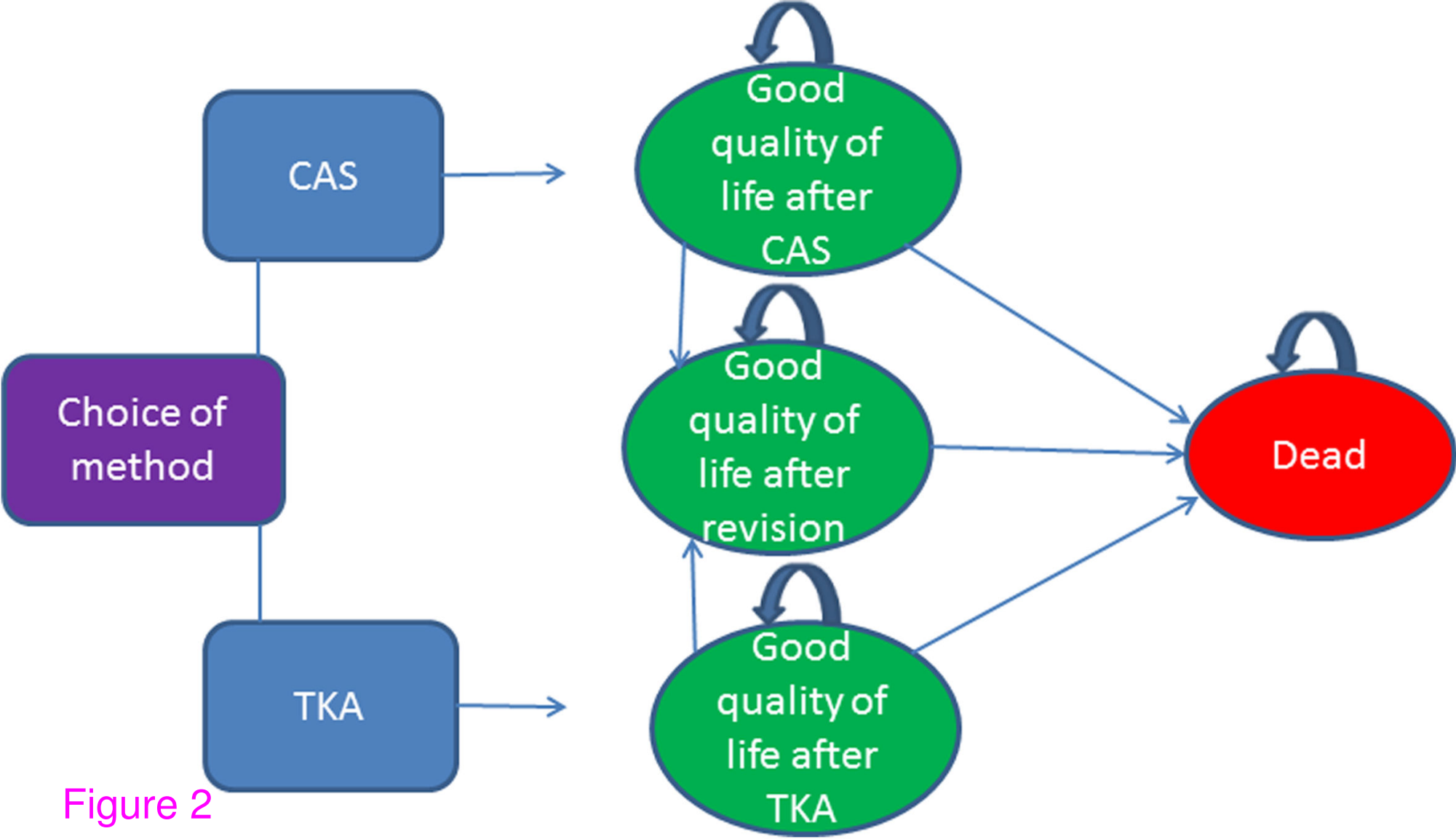

CAS
Choice of method
TKA
Good quality of life after CAS
Good quality of life after revision
Good quality of life after TKA
Dead

Figure 2

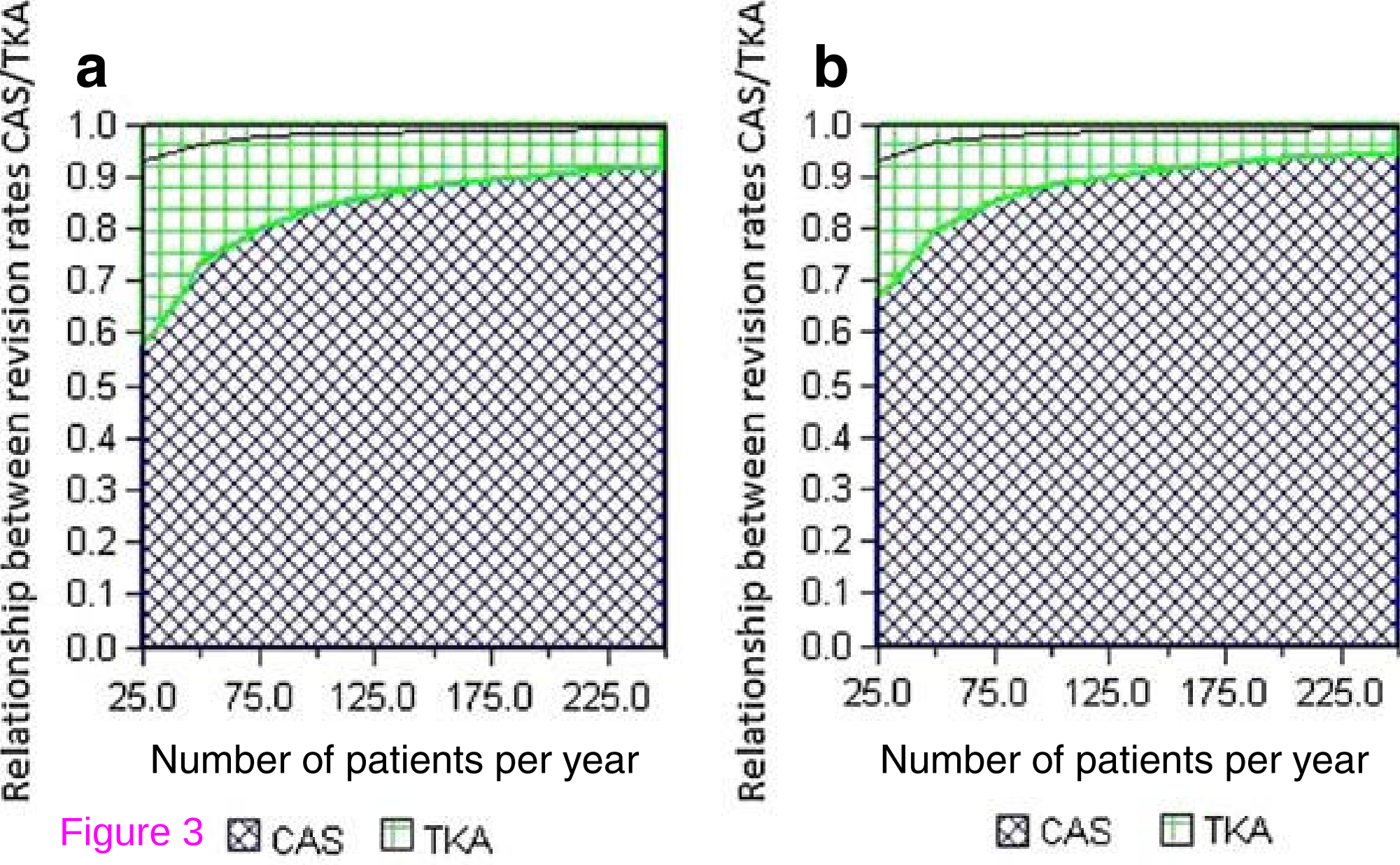

a
b
Relationship between revision rates CAS/TKA
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
25.0
75.0
125.0
175.0
225.0
Number of patients per year
CAS
TKA

Figure 3

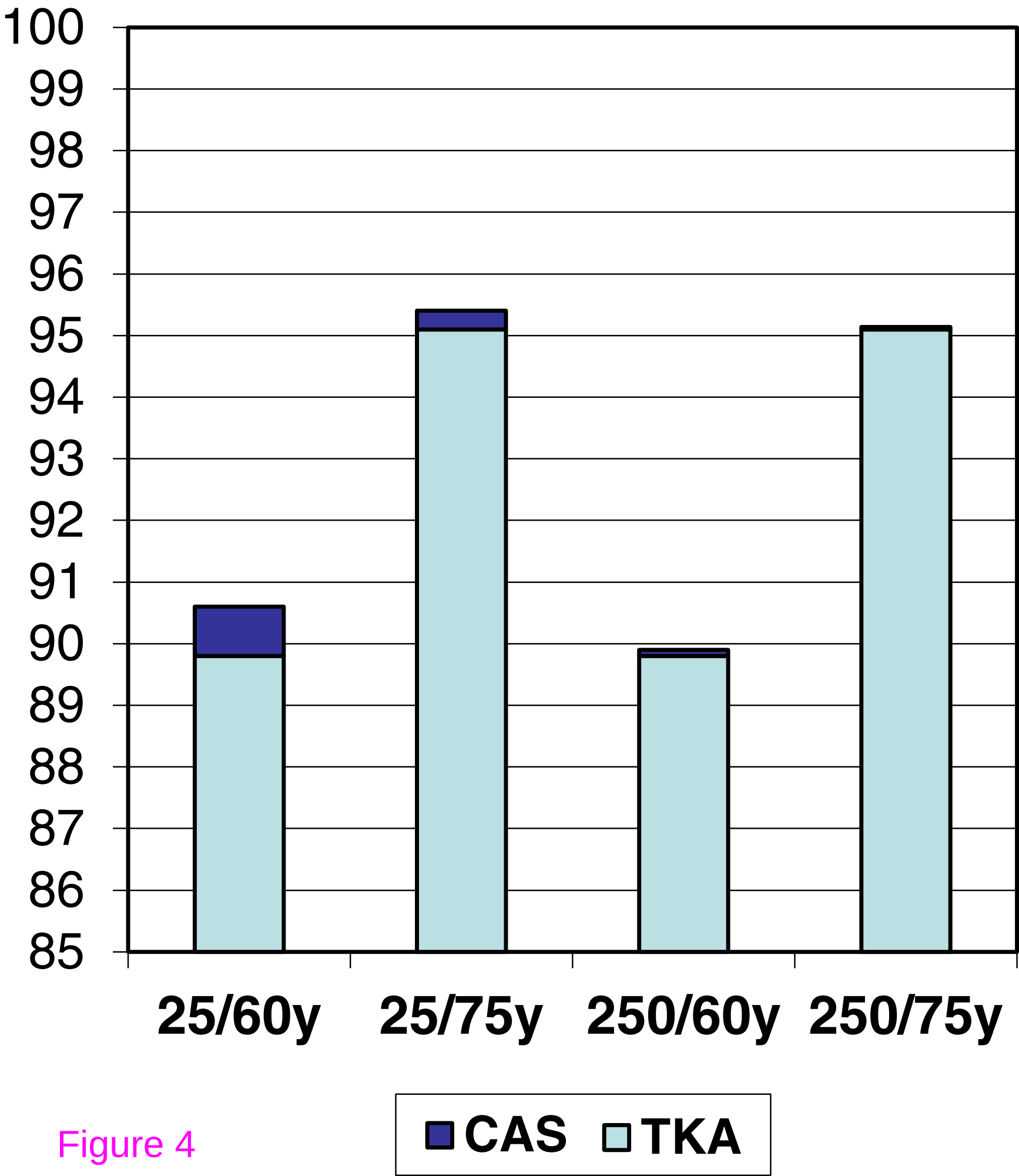

100
99
98
97
96
95
94
93
92
91
90
89
88
87
86
85
25/60y
25/75y
250/60y
250/75y
CAS
TKA

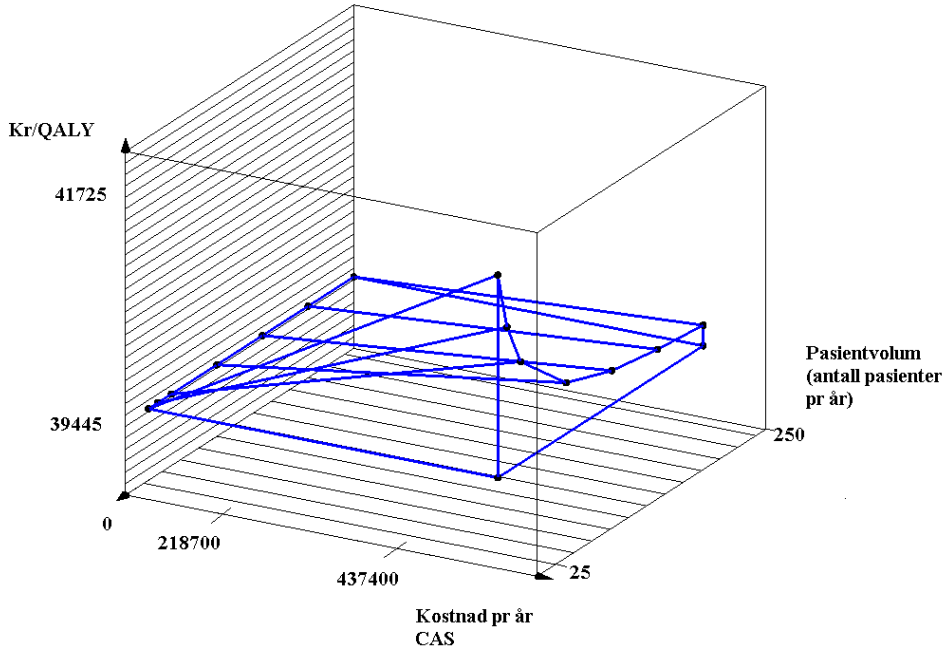
Figure 4

Additional files provided with this submission:

Additional file 1: 2068503638012528_add1.doc, 395K
http://www.biomedcentral.com/imedia/1784813316103010/supp1.doc

Appendix

If we disregard the NOK 500,000 threshold and purely look for the most cost saving (cost effective) alternative, the implant survival rate required to reduce the cost per QALY to the same level as for TKA (table, figure 2-5) will be considerably higher. We would then be assuming that CAS is better than TKA, but that there is no more money available to spend. Given this requirement, the implant survival in cohort 1 will need to increase from 89.8% to 90.6-95.7%, and in cohort 2 from 95.1% to 95.4-97.6%, depending on patient volume and the cost of the navigation equipment (tab 5 below). Again, the requirement for an improved implant survival rate is lowest at high patient volumes. Doubling the cost without a threshold will impact at both high and low patient volumes, with a requirement for further improvement of the 10-year implant survival rate. A somewhat larger reduction of the probability of revision is required in the younger chort (8.0-58.0%) than in the older cohort (5.6-50.0%) in order to achieve the cost reduction (cost effectiveness) required.

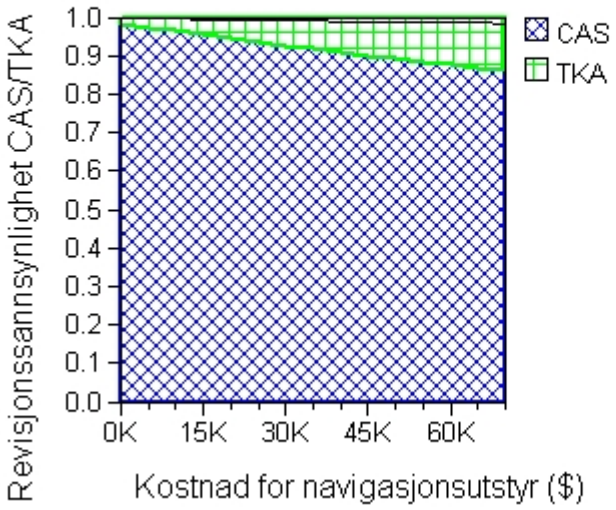


NOK / QUALY

Cost per year, CAS

Patient volume (number of patients per year)

Figure X. 3D diagram showing the connection between increased costs on the X axis, cost per QALY on the Y axis and patient volume on the Z axis for cohort 1.

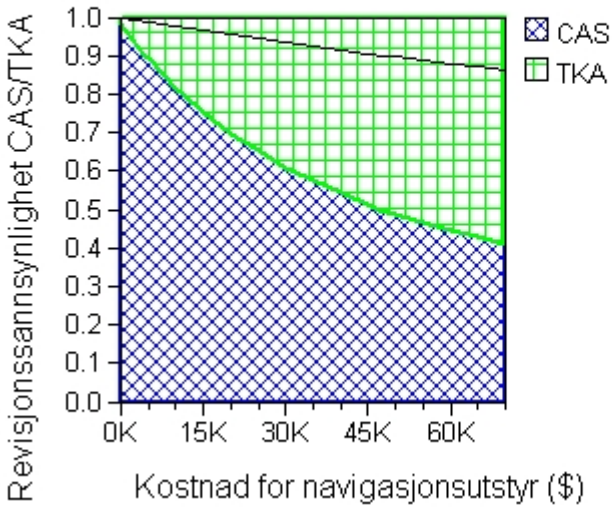


Probability of revision CAS/TKA

Cost of navigation equipment (USD)

Figure 5a (high patient volume, cohort 1, age 60)

We see that at our basic price of USD 33,960 (NOK 216,500), the probability of revision needs to be reduced by 1.0% for the threshold not to be exceeded, and by 8.0% to achieve cost effectiveness. If the costs are doubled the probability of revision needs to be reduced by 1.7% not to exceed the threshold, and 13.5% to achieve cost effectiveness.

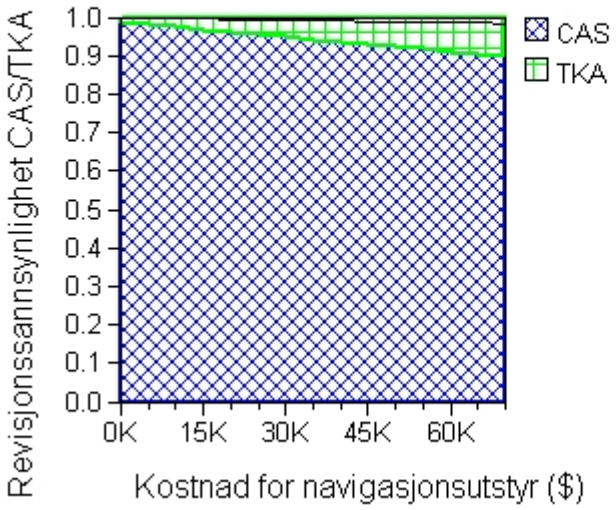


Probability of revision CAS/TKA

Cost of navigation equipment (USD)

Figure 5b (low patient volume, cohort 1, age 60).

We see that at our basic price of USD 33,960 (NOK 216,500) the probability of revision needs to be reduced by 7.5% not to exceed the threshold, and by 42.0% to achieve cost effectivenesss. If the costs are doubled, the probability of revision needs to be reduced by 13.0% not to exceed the threshold, and by 58.0% to achieve cost effectiveness.

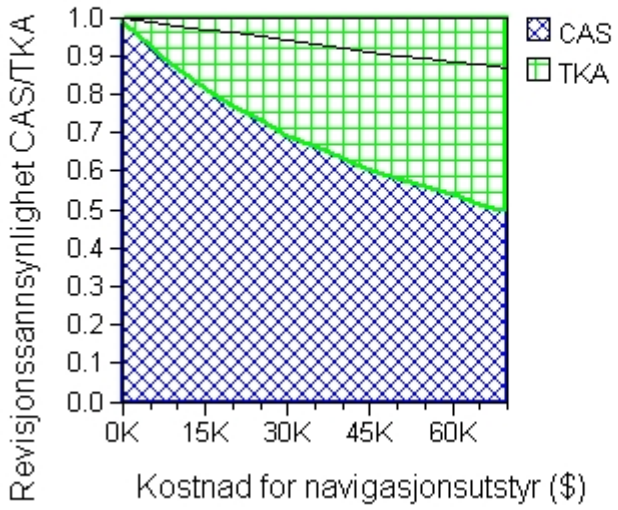


Probability of revision CAS/TKA

Cost of navigation equipment (USD)

Figure 6a (high patient volume, cohort 2, age 75)

Figures 6a and 6b show the impact of costs on cost effectiveness in the older cohort at high and low patient volumes respectively.



Probability of revision CAS/TKA

Cost of navigation equipment (USD)

Figure 6b (low patient volume, cohort 2, age 75)

Index year	Yearly probability of revision <70	Implant survival (Kaplan-Meier) <70	Probability of revision in the course of the first 10 years	Yearly probability of revision >=70	Implant survival (Kaplan-Meier) >=70	Probability of revision in the course of 10 years
1	1.60			1.25		
2	2.30			1.29		
3	1.40			0.79		
4	1.20			0.55		
5	1.00	95.00%		0.52	97.20%	
6	1.05			0.38		
7	1.05			0.37		
8	1.37			0.23		
9	0.70			0.63		
10	0.96	89.75%	10.25	0.25	95.10%	4.90
11	1.02			0.50		
12	0.50			0.50		
13	0.50			0.50		
14	0.50			0.50		
15	0.50	86.75%		0.50	90.10%	
16	1.00			0.50		
17	1.00			0.50		
18	1.00			0.50		
19	1.00			0.50		
20	1.00	81.75%		0.50	85.50%	

Table A. Yearly probability of revision in the two cohorts. Kaplan-Meier implant survival at 5, 10, 15 and 20 years.

60	0.010152	70	0.023668	80	0.057067	90	0.143407
61	0.010869	71	0.025812	81	0.065032	91	0.155088
62	0.012066	72	0.028285	82	0.067581	92	0.167323
63	0.013155	73	0.031088	83	0.077566	93	0.180093
64	0.014333	74	0.033548	84	0.085272	94	0.193378
65	0.015584	75	0.036749	85	0.093544	95	0.207148

66	0.016855	76	0.040177	86	0.102375	96	0.221372
67	0.018535	77	0.043642	87	0.111774	97	0.236010
68	0.020125	78	0.048232	88	0.121744	98	0.251018
69	0.021928	79	0.052885	89	0.132290	99	0.266346
						100	1

Table B. Age-specific death rates. Mortality table 2005, males and females. (Statistics Norway)

Table C. Overview of probabilities of revision and impant survival rates that produce cost effectiveness or that represent the limit for what the healthcare sector is willing to pay (threshold), given the specified prices, patient volumes and age cohorts. (Compared with the current 10-year implant survival rate for 60-year-olds of 89.8% and for 75-year-olds of 95.1%)

		Cost effective					Values indicating the healthcare sector's threshold [3] for willingness to pay			
Cohort 1		High volume[1] Price 1[4]	Low volume[2] Price 1	High volume Price 2[5]	Low volume Price 2		High volume Price 1	Low volume Price 1	High volume Price 2	Low volume Price 2
	Reduction in probability of revision (%)	8.0	42.0	13.5	58.0		1.0	7.5	1.7	13.0
	New 10-year implant survival rate (%)	90.6	94.1	91.2	95.7		89.9	90.6	89.9	91.1
Cohort 2		High volume Price 1	Low volume Price 1	High volume Price 2	Low volume Price 2		High volume Price 1	Low volume Price 1	High volume Price 2	Low volume Price 2
	Reduction in probability of revision (%)	5.6	33.0	10.0	50.0		0.8	7.0	1.5	12.7
	New 10-year implant survival rate (%)	95.4	96.7	95.6	97.6		95.14	95.4	95.2	95.7

[1]250 knee prostheses per year, [2]25 knee prostheses per year, [3]NOK 500,000 per QALY, [4]NOK 216,500, [5]NOK 433,000

Table D. Overview of the connection between changes to utility values following a change in the probability of revision, as well as the impact of age (cohorts 1 and 2) and patient volume on cost effectiveness and the probability of not exceeding the ICER threshold of NOK 500,000.

	Measure of benefit Δ QALY (QALY CAS – QALY TKA)		Cost added and (ICER) per computer assisted knee replacement, given in NOK (cost CAS – cost TKA)			
	Cohort 1 (60-year-olds)	Cohort 2 (75-year-olds)	Cohort 1 (60-year-olds)		Cohort 2 (75-year-olds)	
Reduction in probability of revision (%)			Low volume (25)	High volume (250)	Low volume (25)	High volume (250)
0	0	0	7718	951	7718	951
1	0.001757	0.001760	7609 (4330677)	**843 (479795)**	7562 (4296591)	**795 (451705)**
2	0.003547	0.003552	7499 (2114180)	733 (206654)	7403 (2084178)	636 (179054)
3	0.005372	0.005377	7386 (1374907)	619 (115227)	7240 (1346476)	474 (88153)
4	0.007232	0.007237	7271 (1005393)	505 (69829)	7075 (977615)	309 (42697)
5	0.009129	0.009133	7143 (782452)	388 (42502)	6906 (756159)	139 (15220)
6	0.011063	0.011065	7034 (635813)	268 (24225)	6734 (608586)	**-33 (-2982)**
7	0.013036	0.013035	6912 (530224)	146 (11200)	6558 (503107)	-209 (-16034)
8	0.015050	0.015043	**6788 (451030)**	21 (1395)	**6378 (423985)**	-388 (-25793)
9	0.017104	0.017092	6661 (389441)	**-106 (-6197)**	6195 (362450)	-571 (-33407)
10	0.019202	0.019183	6531 (340121)	-236 (-12290)	6008 (313194)	-758 (-39514)
20	0.042886	0.042693	5060 (117987)	-1707 (-39803)	3882 (90928)	-2885 (-67575)
30	0.072985	0.072300	3177 (43529)	-3590 (-49188)	1151 (15920)	-5615 (-77663)
32	0.080026	0.079177	2734 (34164)	-4033 (-50396)	507 (6403)	-6259 (-79051)
33	0.083699	0.082757	2501 (29881)	-4265 (-50956)	171 (2066)	-6596 (-79703)
34	0.087479	0.086436	2264 (25880)	-4503 (-51475)	**-176 (-2036)**	-6943 (-80325)
36	0.095384	0.094110	1763 (18483)	-5004 (-52462)	-904 (-9606)	-7671 (-81511)
38	0.103784	0.102236	1230	-5536	-302	-8247

			(11852)	(-53342)	(-15777)	(-80666)
40	0.112728	0.110856	661 (5864)	-6105 (-54157)	-2509 (-22633)	-9276 (-83676)
42	0.122271	0.120015	55 (450)	-6715 (-54919)	-3398 (-28313)	-10164 (-84689)
43	0.127287	0.124812	**-270** **(-2121)**	-7037 (-55285)	-3866 (-30975)	-10633 (-85189)
44	0.132477	0.129764	-604 (-4559)	-7371 (-55640)	-4351 (-33530)	-11118 (-85679)
46	0.143417	0.140161	-1310 (-9134)	-8077 (-56318)	-5377 (-38363)	-12144 (-86643)
48	0.155171	0.151271	-2073 (-13359)	-8840 (-56969)	-6486 (-42877)	-13253 (-87611)
50	0.167834	0.163167	-2901 (-17285)	-9667 (-57599)	-7686 (-47105)	-14452 (-88572)
60	0.249111	0.237708	-8387 (-33668)	-15154 (-60833)	-15506 (-65231)	-22273 (-93699)
90	1.017135	0.837304	-80034 (-78686)	-86801 (-85339)	-94317 (-112643)	-101084 (-120726)

Short-term outcome of 1,465 computer-navigated primary total knee replacements 2005–2008

A report from the Norwegian Arthroplasty Register

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Background and purpose Improvement of positioning and alignment by the use of computer-assisted surgery (CAS) might improve longevity and function in total knee replacements, but there is little evidence. In this study, we evaluated the short-term results of computer-navigated knee replacements based on data from the Norwegian Arthroplasty Register.

Patients and methods Primary total knee replacements without patella resurfacing, reported to the Norwegian Arthroplasty Register during the years 2005–2008, were evaluated. The 5 most common implants and the 3 most common navigation systems were selected. Cemented, uncemented, and hybrid knees were included. With the risk of revision for any cause as the primary endpoint and intraoperative complications and operating time as secondary outcomes, 1,465 computer-navigated knee replacements (CAS) and 8,214 conventionally operated knee replacements (CON) were compared. Kaplan-Meier survival analysis and Cox regression analysis with adjustment for age, sex, prosthesis brand, fixation method, previous knee surgery, preoperative diagnosis, and ASA category were used.

Results Kaplan-Meier estimated survival at 2 years was 98% (95% CI: 97.5–98.3) in the CON group and 96% (95% CI: 95.0–97.8) in the CAS group. The adjusted Cox regression analysis showed a higher risk of revision in the CAS group (RR = 1.7, 95% CI: 1.1–2.5; p = 0.02). The LCS Complete knee had a higher risk of revision with CAS than with CON (RR = 2.1, 95% CI: 1.3–3.4; p = 0.004)). The differences were not statistically significant for the other prosthesis brands. Mean operating time was 15 min longer in the CAS group.

Interpretation With the introduction of computer-navigated knee replacement surgery in Norway, the short-term risk of revision has increased for computer-navigated replacement with the LCS Complete. The mechanisms of failure of these implantations should be explored in greater depth, and in this study we have not been able to draw conclusions regarding causation.

The role of computer navigation in knee replacement surgery is still under debate (Bauwens et al. 2007, Kim et al. 2009, Longstaff et al. 2009). Improvement of positioning and alignment by using computer navigation might also improve longevity and function, but there is little evidence. The high costs of computer navigation equipment are inclined to make any improvement less cost-effective (Slover et al. 2008).

Increased costs, the time-consuming nature of the method, and a possible new source of complications—i.e. fractures and infection—are some of the arguments against using computer navigation. In Norway, 11% of the knee replacements performed during 2005–2008 were reported to be implanted using computer navigation (Furnes et al. 2008).

We evaluated the short-term results of computer-navigated primary total knee replacements (CAS) without patella resurfacing, by comparing them to the results of conventionally operated total knee replacements (CON) performed using alignment guides. Revision for any reason was the primary outcome. Intraoperative complications, causes of revision, and operating time were secondary outcomes.

Patients and methods

Primary knee replacements reported to the Norwegian Arthroplasty Register during the period 2005–2008 were included in this prospective observational study. The register was established in 1987 as a hip replacement register (Havelin et al. 2000). The registration of knee replacements started in 1994 (Furnes et al. 2002), but the use of computer navigation was not registered until 2005. At the time of surgery, a form is completed and sent to the register—including information on age, sex, laterality, ASA category, date of surgery, preoperative diagnosis, previous knee surgery, prosthesis type and brand, prophylactic antibiotics, antithrombotic medication, approach

DOI 10.3109/17453674.2011.575743

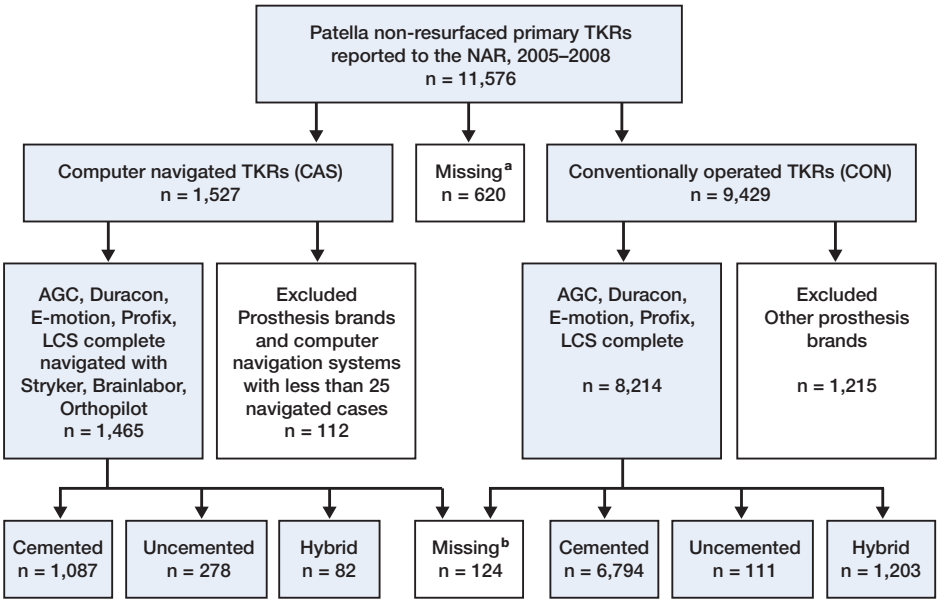

Figure 1. Selection of cases. NAR: Norwegian Arthroplasty Register; TKR: total knee replacement; CAS: computer-assisted surgery (abbreviation for computer-navigated knee replacements in the article), CON: conventionally operated knee replacement, using either intra-medullary or extra-medullary alignment rods.
[a] No information on operative technique.
[b] No information on fixation method.

(minimally invasive or not), surgical method (use of computer navigation or not, and the name of the system being used), fixation method, intraoperative complications, status of the cruciate ligaments, and whether the present operation was a primary or secondary (revision) procedure. Revision is defined as a complete or partial removal/exchange of the implant, or insertion of a component (including patella button). Primary operations were linked to subsequent revisions by the unique identification number of all Norwegian residents. Of all knee replacements performed in Norway, 99% of all primary operations and 97% of all revisions are estimated to be reported to the register (Espehaug et al. 2006).

Selection of patients

11,576 non-patella resurfaced primary total knee replacements implanted during the years 2005–2008 were split into 2 groups: CAS and CON (Figure 1). Patella resurfaced knee replacements were excluded from the material due to low numbers (9 in the CAS group and 241 in the CON group).

In the CAS group, 1,527 operations were performed in 25 orthopedic centers. The number of patients operated with CAS varied from 497 cases reported from 1 center to less than 10 cases, reported from each of 7 centers. 4 computer navigation systems (Brainlab, Orthopilot, Aculumen, and Stryker) and 10 different implants with cemented, uncemented, and hybrid fixation were reported. Only 19 knees were computer-navigated with the use of Aculumen, and they were excluded due to the small number. We selected the 3 most frequently used navigation systems (Brainlab, Orthopilot, and Stryker), along with the 5 most frequently used computer-navigated implants (AGC: Biomet; Duracon: Stryker; e.motion: Aesculap, LCS Complete: DePuy; and Profix: Smith and Nephew) (Figure 1). Implants inserted with a computer-navigated system less than 25 times were excluded, leaving 1,465 computer-navigated knees that were suitable for evaluation.

In the CON group, 9,429 implantations were performed during this time period. From these implantations, only the same prosthesis brands as in the CAS group were selected, giving 8,214 CON knee replacements for comparison.

Demographics

In the CAS group, there were more males and they were 1 year younger on average than in the CON group (Table 1). Intraoperatively verified deficiency of the ACL, previous surgery of the knee, and the use of uncemented implants were more frequent in the CAS group.

Statistics

Descriptive analyses were performed to assess baseline characteristics of the study groups. Differences were evaluated using the chi-square test for proportions and the independent-samples t-test for mean values.

The CON group was compared to the CAS group regarding survivorship. Revision for any reason—and secondly, revision due to specific causes—was used as endpoint. Information on deaths or emigrations was retrieved from the National Population Register until December 31, 2009. The survival times of unrevised implants were censored at the last date of observation, meaning the date of death or emigration, or December 31, 2009. Median follow-up was calculated following the reverse Kaplan-Meier method (Schemper and Smith 1996). The Kaplan-Meier method provided unadjusted estimates of survivorship after 1 and 2 years of follow-up. The Cox multiple regression model was used to calculate hazard rate ratios (RRs) for evaluation of the effect of computer navigation on survivorship, with adjustment for potential confounding by age (continuous), sex, ASA category (I, II, III/IV), method of fixation (cemented, uncemented, or hybrid cementation (uncemented femur, cemented tibia)), prosthesis brand, preoperative diagnosis (osteoarthritis, other diagnoses), and previous knee surgery (yes/no). The adjusted RR estimates are presented with 95% confidence intervals (CIs) and p-values relative to the CON group. Additional adjustment for operating time did not alter the

Table 1. Demographic data of primary total knee replacements without patella component (computer navigated (CAS) or conventionally operated (CON)) reported to the Norwegian Arthroplasty register, 2005–2008

	CAS	CON	p-value
Number	1,465	8,214	
Men %	39	33	< 0.001
Age, years	68.8	69.8	0.001
95% CI	68.3–69.3	69.5–70.0	0.001
Right knee, %	56	55	0.3
MIS [a], % (n)	0 (7)	0 (21)	< 0.001
ASA category [b], % (n)			0.03
1	19 (272)	22 (1,766)	
2	62 (907)	57 (4,706)	
3	18 (266)	20 (1,630)	
4	0 (2)	0 (14)	
missing	1 (18)	1 (98)	
Diagnosis preoperatively, %			
Primary gonarthritis	90	89	0.1
Other	10	11	
Fixation method, % (n)			< 0.001
Cemented	75 (1,087)	84 (6,794)	
Uncemented	19 (278)	1 (111)	
Hybrid (uncemented femur)	6 (82)	15 (1,203)	
Prosthesis brand, % (n)			< 0.001
AGC	5 (80)	13 (1,072)	
Duracon	11 (168)	5 (443)	
e.motion	21 (300)	0 (7)	
LCS complete	39 (570)	35 (2,834)	
Profix	24 (347)	47 (3,858)	
Prosthesis design, % (n)			
Fixed bearing	41 (595)	65 (5,373)	< 0.001
Mobile bearing	59 (870)	35 (2,841)	< 0.001
Stabilized [c]	2 (25)	2 (174)	0.2
Previous operations of the knee, %	37	27	< 0.001
Osteosynthesis affecting the knee joint	3	2	0.02
Osteotomy	5	4	0.3
Synovectomy	2	2	0.9
Other	30	21	< 0.001
Intact ACL[d] preoperatively, %	71	81	< 0.001

[a] MIS: minimally invasive surgery.
[b] ASA category: American Society of Anesthesiologists physical status classification system.
[c] Polyethylene insert posteriorly stabilized or other stabilization.
[d] ACL: anterior cruciate ligament.

RR estimates. Cox regression with use of computer navigation as stratification factor was used to construct survival curves for the treatment groups, with adjustment for the factors described above. Survival curves for the various prosthesis brands were constructed in the same way. In subanalyses, results of computer-navigated and conventionally operated knees were obtained for each prosthesis brand and also according to fixation method (cemented knee replacements, uncemented knee replacements, and hybrid knee replacements).

The proportional hazards assumption of the Cox model was tested based on scaled Schoenfeld residuals (Grambsch 1995). The analysis showed that the assumption was valid for the treatment group (p = 0.1). Furthermore, the assumption of independent observations may be questioned since some patients with operations in both knees were included (bilateral observations, 9%). However, several studies have found that the effect of including bilateral operations on the results is minor—both for hip prostheses (Lie et al. 2004) and for knee prostheses (Robertsson and Ranstam 2003).

In a subanalysis, a possible effect of a learning curve was investigated by excluding the first 20 operations with CAS at each center. The specific results of each center were investigated and the impact of hospital volume was addressed in a separate subanalysis, by selecting centers with more than 50 CAS cases. Furthermore, a selection of centers performing both operating techniques in the same time period was analyzed.

Secondary outcome measures were investigated using Fisher's exact test for comparison of intraoperative complication rates and the independent-samples t-test for mean operating times.

Statistical significance was set at 0.05. The analyses were done using SPSS software version 17.0 and R (the R Foundation for Statistical Computing).

Follow-up

The mean follow-up time was 1.4 years in the CAS group and 1.8 years in the CON group.

Ethics

The Norwegian Arthroplasty Register has permission from the Norwegian Data Inspectorate to collect patient data, based on obtaining written consent from patients (last issued May 24, 2004; reference number 2003/58-3).

Results

Overall survivorship (Table 2)

The CAS group had a higher risk of revision than the CON group (Figure 2). At 1 year, the survival rate was 98.8% (CI: 98.6–99.0) in the CON group and 98.5% (CI: 97.7–99.3) in the CAS group. At 2 years, the survival rates were 97.9% (CI: 97.5–98.3) in the CON group and 96.4% (CI 95.0–97.8) in the CAS group. Cox regression analysis, adjusting for age, sex, prosthesis brand, ASA category, preoperative diagnosis, previous knee surgery, and fixation method, showed a higher relative risk of revision in the CAS group than in the CON group (RR = 1.7, CI: 1.1–2.5; p = 0.02).

Prosthesis brands (Figure 3)

The mobile-bearing LCS Complete in particular (with all methods of fixation) had a higher risk of revison when inserted with computer-assisted navigation (n = 570) than when inserted by conventional means (n = 2,834) (RR = 2.1, CI: 1.3–3.4; p = 0.004). For the AGC implant (with 80 CAS and 1,072 CON) and the Duracon implant (168 CAS and 443 CON), the relative risks were 1.8 (CI: 0.4–8.0; p = 0.4) and 1.4 (CI: 0.4–5.7; p = 0.6) in favor of the CON group, but there were few revisions

Table 2. Kaplan-Meier survivorship (KM) and adjusted Cox regression relative risk for conventionally operated (CON) and computer-navigated (CAS) primary total knee replacements without patella resurfacing reported to the Norwegian Arthroplasty Register, 2005–2008

	Revised/ total (%)	MF [a] (years)	1 year At risk	1 year KM survival (95% CI)	2 years At risk	2 years KM survival (95% CI)	2005–2008 Cox-adjusted [b] relative risk (95% CI)
CON	149/8,214 (1.8%)	1.8	5,776	98.8 (98.6–99.0)	3,520	97.9 (97.5–98.3)	1
CAS	32/1,465 (2.2%)	1.4	757	98.5 (97.7–99.3)	400	96.4 (95.0–97.8)	1.7 (1.1–2.5) [c]

[a] MF: mean follow-up (reversed KM).
[b] Adjusted for sex, age, prosthesis brand, preoperative diagnosis, previous knee surgery, fixation method, and ASA category.
[c] P-value = 0.019

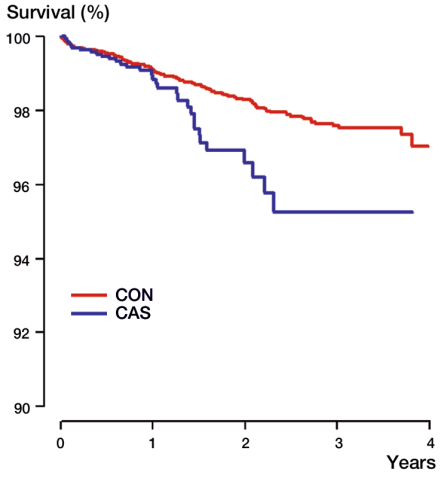

Figure 2. Cox regression survival curves of computer-navigated (CAS) and conventionally operated (CON) primary total knee replacements, without patella resurfacing, reported to the Norwegian Arthroplasty Register 2005–2008.

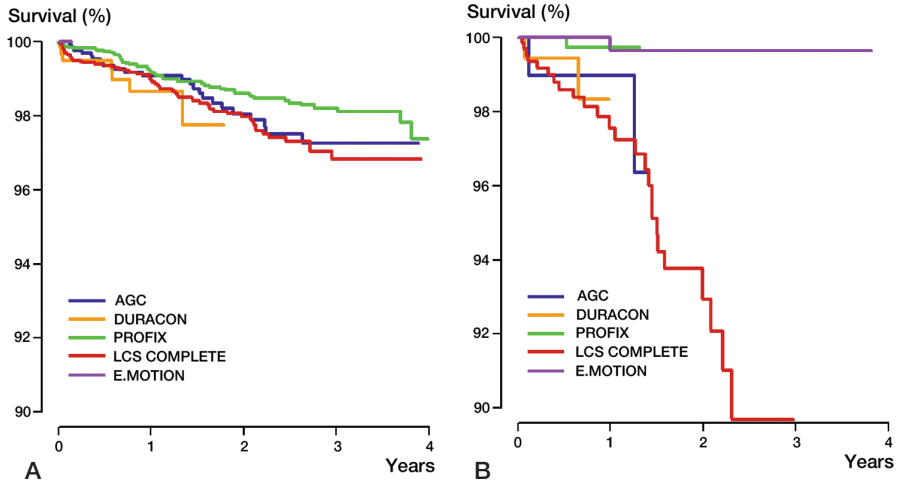

Figure 3. A. Cox regression survival curves of conventionally operated knee replacements (CON) sorted into various prosthesis brands, as reported to the Norwegian Arthoplasty Register 2005–2008. B. Cox regression survival curves of computer-navigated knee replacements (CAS) sorted into various prosthesis brands.

and the finding was not statistically significant. A subanalysis of the AGC Anatomic did not show significantly altered results (RR = 1.7, CI: 0.4–7.8; p = 0.5). The Profix (347 CAS and 3,858 CON) appeared to have a lower relative risk (RR = 0.8, CI: 0.1–5.6; p = 0.8) when computer navigated, not statistically significant. Only 1 of the 300 mobile-bearing e.motion knee replacements that was inserted using computer-assisted navigation was revised.

Fixation method

When only cemented implants were selected (1,087 CAS and 6,794 CON), the relative risk of revision was similar, with a higher risk in the CAS group (RR = 1.8, CI: 1.1–2.8; p = 0.02). Separately, the cemented mobile bearing LCS Complete (421 CAS and 2,521 CON) still had a higher risk of revision in the computer-navigated group (RR = 2.0, CI: 1.3-3.3; p = 0.005).

For the uncemented implants (278 CAS and 111 CON) we found the same tendency, but this was not statistically significant (RR = 1.7, CI: 0.6–4.6; p = 0.3). All revisions in the uncemented group involved the LCS Complete brand. In the hybrid knee replacements (uncemented femur and cemented tibia: 81 CAS and 1,201 CON), the tendency of an inferior outcome for the CAS knees prevailed, but the result was not statistically significant (RR = 3.5, CI: 0.4–31; p = 0.3).

Intraoperative complications (Table 3)

The frequency of intraoperative complications was similar in both groups. Complications occurring with a frequency of more than 1 in 1,000 cases were included in the analysis. The complications reported were too few to reveal any statistically significant differences, except in the category “anesthesia failure”, which was not reported in the CON group but was reported 3 times in the CAS group.

Causes of revision (Table 4)

There was a tendency of more revisions due to deep infection (RR = 1.7, CI: 0.9–3.3; p = 0.1) and loosening of the tibia (RR = 2.1, CI: 0.9–4.9; p = 0.1) in the CAS group, when adjusting

Table 3. Intraoperative complications occurring more frequently than 1 in 1,000

	Instrument failure	Fracture of the tibia	Cement failure	Anesthesia failure	Torniquet failure	Patella tendon rupture/avulsion or ligamentous/tendinous injury
CON	10	15	6	0	8	21
CAS	5	4	3	3	3	4
p-value [a]	0.1	0.5	0.1	0.003	0.2	0.8

[a] By Fisher's exact test.

Table 4. Total knee replacements reported to the Norwegian Arthroplasty Register, 2005–2008: causes of revision and Cox relative risk (RR) with 95% CI. Computer-navigated TKRs (CAS) and conventionally operated TKRs (CON) are compared. (There may have been more than one cause of revision reported in each case)

	A	B	C	D	E	F	G	H	I	J	K	L
CON, n	8	22	3	4	22	11	36	6	63	6	19	149
CAS, n	0	8	1	0	2	1	13	1	13	0	1	32
RR CAS vs CON (95%CI)	–	2.1 0.9–4.9	2.4 0.2–25	–	0.6 0.1–2.4	0.7 0.1–5.6	1.7 0.9–3.3	0.9 0.1–7.7	1.3 0.7–2.5	–	0.3 0.04–2.2	

A Loose femoral component
B Loose tibial component
C Dislocated patella
D Dislocation (not patella)
E Instability
F Malalignment
G Deep infection
H Fracture (affecting implant)
I Pain
J Defect polyethylene insert
K Other
L Total no. revised

for age and sex, but the number of revisions was low and the differences were not statistically significant. Revisions due to malalignment (RR = 0.7, CI: 0.1–5.6; p = 0.7) and instability (RR = 0.6, CI: 0.1–2.4; p = 0.4) were more frequent in the CON group, but this was not statistically significant.

Learning curve

When the first 20 operations at each center were excluded, the relative risk was 1.8 (CI: 1.1–2.9; p = 0.02) in favor of the CON group, which was similar to the risk without the exclusion.

Hospital volume and hospital-specific results

When we selected centers performing more than 50 operations with the use of computer navigation, the number of CAS knees was reduced to 1,221, and the statistical power was weaker. There was a tendency of inferior results for the CAS group (RR = 1.4, CI: 0.8–2.6; p = 0.2).

The hospitals performing both techniques were suitable for a direct comparison of the 2 groups. We found the same increased relative risk for the CAS group (RR = 1.6, CI: 1.0–2.6; p = 0.05). When each hospital was checked individually to reveal any difference in survivorship between the CON and CAS groups, the numbers were small and no statistically significant differences were found.

Operating time

The mean operating time was 107 (SD 33) min in the CAS group and 92 (SD 29) min in the CON group (p < 0.001).

Discussion

We found that the 2-year risk of revision was higher for the CAS group than for the CON group. Consequently, the effect of improved alignment by computer-assisted navigation on the long-term survivorship must be even greater than previously suggested (Slover et al. 2008) in order to achieve cost-effectiveness with CAS.

Strengths and limitations

The large number of surgeons and hospitals participating at the national level was a strong point of this study, and resulted in good external validity. The outcome is probably what could be expected by the average surgeon. Previous studies on computer navigation have been done at expert centers with one or a few

enthusiastic surgeons, and the main outcome has been alignment. In the present study we concentrated on the clinically important risk of revision and the various reasons for revision.

The number of knee implants that are inserted by computer-assisted navigation in Norway is small, but the number is still sufficient to show statistically significant inferiority of CAS compared to CON, with short-term follow-up. Not all centers performing the operations have been using both methods, so we did a subanalysis to include only centers using both methods over the study period, to allow a more direct comparison. The results of the subanalysis were in favor of CON, but this was not statistically significant. A randomized clinical trial would typically address this problem by comparing the 2 groups directly, with standardized perioperative facilities. On the contrary, a registry study will reflect the results in a general population, with average surgeons and a regular perioperative set-up. The applicability and external validity might be regarded as stronger with a registry study, involving many surgeons from different types of centers and different prostheses, surgical techniques, and experience—and with a higher power to detect differences due to a higher number of patients (Graves 2010).

Considering the fact that 20% of the knee replacements performed in Norway in 2008 were computer-navigated, the inferior short-term results give cause for concern.

Explanations and mechanisms

1,465 knees is not a large number from a registry point of view, and may have introduced some bias into the results. A learning curve and technical failures related to the computer navigation systems would be expected to negatively affect the survivorship, but exclusion of the first 20 operations at each center did not alter our results. Interestingly, Maniar et al. (2011) found that there was a learning curve with the use of computer navigation, but even patients who were operated during the period of the surgeon's learning curve achieved a better alignment with the navigation technique than with the conventional technique. The outcome, however, was radiographic alignment and not short-term survivorship. The learning curve might involve technical difficulties that compromise the bones, ligaments, soft tissue, and fixation method, which would not be revealed on postoperative radiographs. We regarded 20 patients as representing a reasonable learning curve, but the curve might be steep even after 20 operations, and in some centers these operations are perhaps performed by more than one surgeon with different skills and experience. Insufficient training programs for CAS might lead to a long learning curve with increased complication rates. Perhaps the technical failures related to computer navigation are difficult to avoid—even for experienced surgeons. Our study suggests that there are indeed some technical failures typically related to the computer navigation technique, which may compromise the survivorship. Specifically, the prolonged operating time and the disadvantage of trans-cortical drilling of the tibia and femur to fix the trackers to the bone are of concern (Jung et al. 2007, Bonutti et al. 2008, Li et al. 2008). In our study, there was no evidence of an increased risk of fracture with the use of computer navigation. However, fractures not leading to removal of the implant, or parts of an implant, are not reported to the register unless they occur as an intraoperative complication. Theoretically, the observed prolongation of operating time might increase the risk of revision due to infection, as previously reported for hip replacements (Smabrekke et al. 2004). In our study, however, the prolonged operating time did not give any increased risk of infection. In a separate survival analysis we adjusted for operating time, but the difference in survivorship remained, in favor of CON, indicating that infection was not a major cause of the inferior survivorship in the CAS group.

Our findings also suggest that there are brand-specific problems when matching computer navigation systems and prosthesis brands. The most frequently revised prosthesis brand in the CAS group was the mobile bearing LCS Complete, with survivorship inferior to that of the LCS Complete in the CON group. Thus, our finding might suggest that the LCS Complete is difficult to navigate, perhaps due to the mobile bearing design of the implant or to the brand-specific surgical instruments using gap-measuring technique. The fixed-bearing Profix prosthesis is computer-navigated with the same "open" system (Brainlab) as the LCS Complete, but this combination was not inferior to the conventionally operated Profix knee. Furthermore, the LCS Complete and the e.motion prostheses both have a mobile-bearing polyethylene, but the e.motion—which is closely linked to the "closed" Orthopilot navigation system—had excellent survivorship, with only 1 revision. Thus, the compatibility between computer navigation system and prosthesis brand might be important. "Open" systems are not matched for one prosthesis brand only, but seek to embrace all kinds of implants. "Closed" systems may be more closely matched to the implants, which could be an advantage.

Comparison with other relevant studies

Our study reveals that unexpected problems may occur when new technology is introduced onto the market. Previous reports have discussed how much of an improvement is needed to render this new procedure cost-effective (Novak et al. 2007, Slover et al. 2008). In contrast, we found that the short-term results on a national basis were inferior with the use of this new technology, thus changing the outlook on whether this technology really is an improvement after all. New kinds of complications may not only neutralize the effect of a better alignment, but might even negatively affect the long-term survivorship.

Some authors have suggested that computer navigation is most helpful in difficult cases with malalignment, fracture sequelae, and abnormal anatomy (Laskin and Beksac 2006). Surgeons may then have selected difficult cases for computer navigation, which could have affected our results. We have adjusted for differences between the two groups, but preop-

erative malalignment data were not available for analysis. If the most malaligned knees were selected for computer navigation, inferior results might be more likely to occur. This issue should be explored further in randomized clinical trials with long-term follow-up.

Intraoperative complications were similar in both groups, except that "anesthesia failure" was reported 3 times in the computer navigated group and never in the conventionally operated group. This failure might be due to the longer operating time, with loss of spinal anesthesia. Revisions because of malalignment or instability were more frequent, although not statistically significantly so, in the CON group. The computer navigation was primarily introduced to knee replacement surgery to improve the alignment, so this finding was not surprising. The instability might be due to ligamentous imbalance and malaligned implantations (Gorab and Barnett 2002), but again, our numbers were too small to allow us to make any conclusions.

Possible implications

The introduction of new risk factors with CAS and compatibility problems between CAS systems and specific prosthesis brands could indicate more restricted use of the CAS technology. The results with specific prosthesis brand results were divergent, however, and some brands may have benefited from this new technology while others had inferior results with the use of computer navigation. The explanation for the inferior results with CAS, especially for the LCS Complete, might not only be problems with the computer navigation technology, but they could also be a result of surgical errors introduced along with this new technique. A selection bias from recruiting difficult patients to the CAS group is another explanation that cannot be overlooked, even though we tried to adjust for differences between the groups. Development of faster computer navigation techniques with more user-friendly instruments might improve the short-term results. Long-term registry studies and large randomized clinical trials with a long-term follow-up will be necessary to verify our findings and to explore the failure mechanisms in more detail. However, the rapid evolution of new technology challenges our standards and demands faster evaluation methods. Radiostereometric analysis (RSA) and laboratory tests are some ways of speeding up the evaluation process.

Conclusion

With the introduction of computer navigation to knee replacement surgery in Norway, the short term risk of revision has increased for the LCS complete implant. Even though the difference is small, improved longevity due to CAS might be unlikely, considering the inferior short term results. The failure mechanisms of these implantations must be explored in greater detail, and we have not been able to draw any conclusions from the present study regarding causation. The success of computer navigation as a surgical instrument may be dependent on the design of the implant; selection bias and the introduction of surgical errors may affect the results. Thus, care has to be taken when introducing new technology into a field of orthopedics where the results are already good.

Study design and statistical analysis: OG, BE, and OF. Evaluation of clinical relevance concerning methods and statistical analayses: OG, BE, GP, LH, and OF. Preparation of manuscript and evaluation of clinical relevance concerning methods and statistical analyses: OG, BE, GP, LH and OF

Thanks to all the orthopedic surgeons in Norway who have contributed to the unique database at the Norwegian Arthroplasty Register with excellent and accurate reporting of their operations.

No competing interests declared.

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■ KNEE

Survival rates and causes of revision in cemented primary total knee replacement

A REPORT FROM THE NORWEGIAN ARTHROPLASTY REGISTER 1994–2009

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doi:10.1302/0301-620X.95B5.30271 $2.00

Bone Joint J 2013;95-B:636–42.
Received 14 June 2012; Accepted after revision 11 January 2013

We evaluated the rates of survival and cause of revision of seven different brands of cemented primary total knee replacement (TKR) in the Norwegian Arthroplasty Register during the years 1994 to 2009. Revision for any cause, including resurfacing of the patella, was the primary endpoint. Specific causes of revision were secondary outcomes.

Three posterior cruciate-retaining (PCR) fixed modular-bearing TKRs, two fixed non-modular bearing PCR TKRs and two mobile-bearing posterior cruciate-sacrificing TKRs were investigated in a total of 17 782 primary TKRs. The median follow-up for the implants ranged from 1.8 to 6.9 years. Kaplan-Meier 10-year survival ranged from 89.5% to 95.3%. Cox's relative risk (RR) was calculated relative to the fixed modular-bearing Profix knee (the most frequently used TKR in Norway), and ranged from 1.1 to 2.6. The risk of revision for aseptic tibial loosening was higher in the mobile-bearing LCS Classic (RR 6.8 (95% confidence interval (CI) 3.8 to 12.1)), the LCS Complete (RR 7.7 (95% CI 4.1 to 14.4)), the fixed modular-bearing Duracon (RR 4.5 (95% CI 1.8 to 11.1)) and the fixed non-modular bearing AGC Universal TKR (RR 2.5 (95% CI 1.3 to 5.1)), compared with the Profix. These implants (except AGC Universal) also had an increased risk of revision for femoral loosening (RR 2.3 (95% CI 1.1 to 4.8), RR 3.7 (95% CI 1.6 to 8.9), and RR 3.4 (95% CI 1.1 to 11.0), respectively). These results suggest that aseptic loosening is related to design in TKR.

Cite this article: *Bone Joint J* 2013;95-B:636–42.

The aim of this study was to investigate the rate of survival and causes of revision for seven brands of cemented primary total knee replacement (TKR) registered in the Norwegian Arthroplasty Register (NAR) between 1994 and 2009. The brands are currently and historically among the most commonly used both in Norway and around the world.[1,2] The study was limited to cemented implants without patellar resurfacing, and the data reflect the results of the average surgeon. We accept that pooling of data from many surgeons, with different experience, patient volumes and skills, may give good external validity but may also hide the effect of a learning curve and any positive effect that may be related to high volumes undertaken by some surgeons.

We also investigated whether survival was brand specific or related to particular types of design.

Patients and Methods

Data from patients registered in the NAR during this time were evaluated. The registration of hip replacements in the NAR started in 1987 and was expanded to include TKRs and the replacement of other joints in 1994.[3,4] The completeness of the registration was estimated by Espehaug et al[5] to be 99% of all primary TKRs and 97% of all revision procedures between 1999 and 2002. Any complete or partial removal/exchange of the implant, or insertion of a component (including a patellar component), was considered a revision procedure. The unique identification number of all Norwegian residents facilitates linking the revisions to the primary operations.

All TKRs were cemented and were inserted without patellar components. Differences between the designs were predominantly on the tibial side; two were mobile-bearing TKRs (LCS Classic and LCS Complete (DePuy, Warsaw, Indiana), both rotating platform), two were non-modular fixed bearing TKRs (AGC Universal and AGC Anatomic; both Biomet, Warsaw, Indiana), and three were modular fixed-bearing TKRs (Duracon; Stryker, Portage, Michigan; NexGen; Zimmer, Warsaw, Indiana; and Profix; Smith & Nephew, Memphis, Tennessee). The mobile-bearing TKRs were posterior cruciate ligament (PCL) sacrificing, and the others were PCL retaining.

Implant designs not in use after 2004, and those that were used in < 500 cases, were

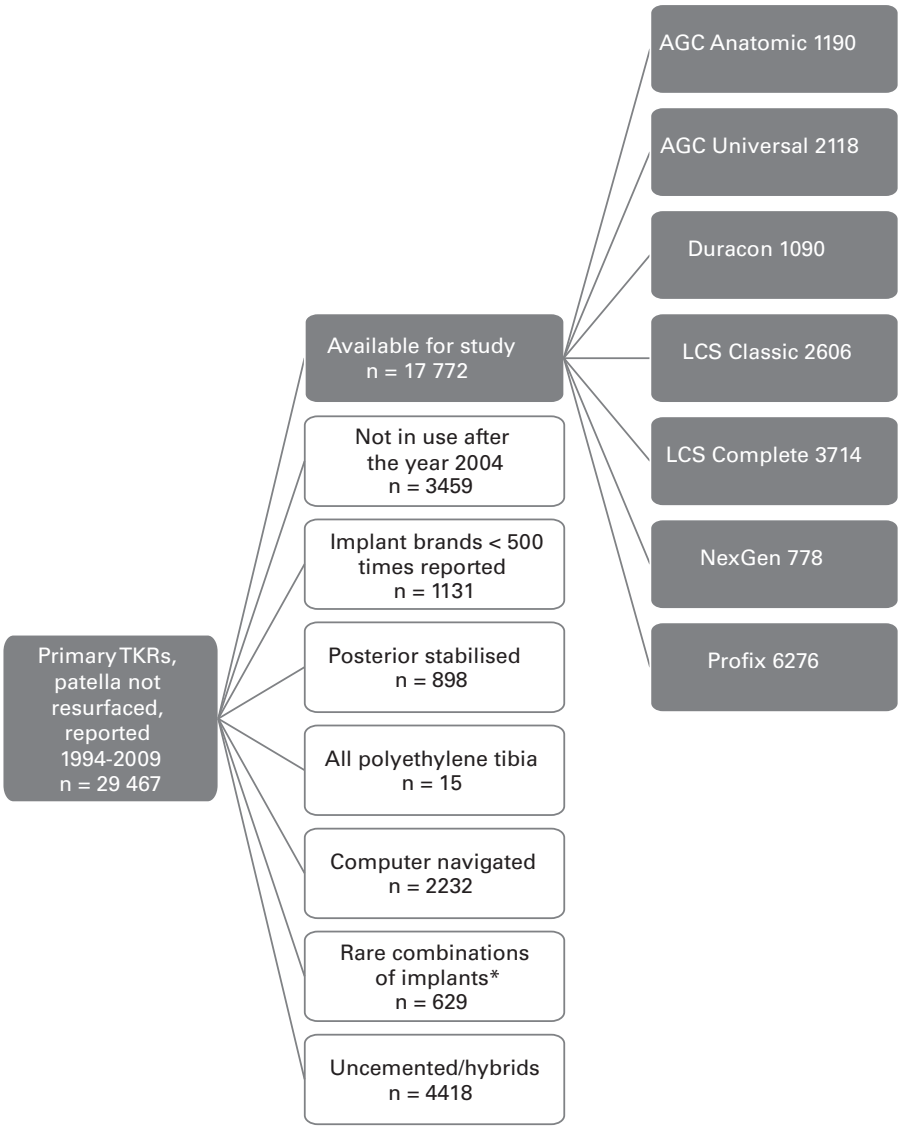

Fig. 1

Selection chart showing inclusions and exclusions of cases. There may be more than one exclusion criterion per case (* rare combinations of implants: Profix mobile-bearing (n = 12), AGC Dual (52), various combinations of LCS (n = 565); TKR, total knee replacement).

excluded (Fig. 1). TKRs introduced with computer-navigation were excluded because the technique was not widely used for the TKRs that were selected. Posterior-stabilised implants were excluded because of relatively low numbers (the Profix Conforming Plus was regarded as posterior stabilised). The inclusion criteria were met by 2118 AGC Universal, 1190 AGC Anatomic, 1090 Duracon, 778 NexGen, 6276 Profix, 2606 LCS Classic and 3714 LCS Complete TKRs.

Statistical analysis. Revision for any cause was the primary endpoint. Specific causes for revision and types of revision were secondary outcomes. Descriptive analyses were used to assess the baseline characteristics of the various brands (Table I). Information on deaths or emigrations up to 31 December 2009 was retrieved from the National Population Register. The survival times of unrevised TKRs were taken at the last date of observation (date of death or emigration, or 31 December 2009). Median follow-up was calculated with the reverse Kaplan–Meier method.[6] Unadjusted survival curves for the various brands were constructed using the Kaplan-Meier method, and stopped when < 50 knees remained at risk. Survival percentages after five and ten years' follow-up are reported. Cox's multiple regression model was used to calculate hazard rate ratios (RR), adjusted for potential confounding by age, gender, pre-operative diagnosis (osteoarthritis or other diagnoses) and previous knee surgery (yes/no). The RR estimates are presented with 95% confidence intervals (CI) and p-values reported relative to the Profix TKR, which was the most common

Table I. Demographic data (ACL, anterior cruciate ligament; PCL, posterior cruciate ligament)

	Implant						
Characteristic	**AGC Anatomic**	**AGC Universal**	**Duracon**	**LCS Complete**	**LCS Classic**	**NexGen**	**Profix**
Patients (n)	1190	2118	1090	3714	2606	778	6276
Male (n, %)	450 (*37.8*)	650 (*30.7*)	352 (*32.3*)	1219 (*32.8*)	718 (27.6)	273 (*35.1*)	1950 (*31.1*)
Right knee (n, %)	637 (*53.5*)	1149 (*54.2*)	596 (*54.7*)	2004 (*54.0*)	1437 (*55.1*)	394 (*50.6*)	3422 (*54.5*)
Mean (SD) age (yrs)	69.7 (9.1)	71.0 (9.2)	70.7 (9.3)	69.6 (9.6)	71.5 (9.0)	69.2 (10.5)	70.0 (10.0)
Age group (n, %)							
≤ 60 years	169 (*14.2*)	259 (*12.2*)	141 (*12.9*)	597 (*16.1*)	299 (*11.5*)	130 (*16.7*)	1015 (*16.2*)
61 to 70 years	393 (*33.0*)	575 (*27.1*)	330 (*30.3*)	1214 (*32.7*)	706 (*27.1*)	235 (*30.2*)	1846 (*29.4*)
71 to 80 years	492 (*41.3*)	962 (*45.4*)	446 (*40.9*)	1394 (*37.5*)	1174 (*45.0*)	316 (*40.6*)	2434 (*38.8*)
> 80 years	136 (*11.4*)	322 (*15.2*)	173 (*15.9*)	509 (*13.7*)	427 (*16.4*)	97 (*12.5*)	981 (*15.6*)
Diagnosis (n, %)							
Primary osteoarthritis	1062(*89.5*)	1832 (*86.9*)	950 (*87.5*)	3338 (*90.1*)	2268 (*87.4*)	674 (*86.7*)	5325 (*85.2*)
Other	124 (*10.5*)	276 (*13.1*)	136 (*12.5*)	366 (*9.9*)	328 (*12.6*)	103 (*13.3*)	928 (14.8)
Hospitals using this design (n)	11	29	18	35	30	19	40
Mean (SD) operation time (min)	85 (23)	96 (23)	98 (30)	97 (24)	101 (35)	105 (54)	92 (32)
Cement with antibiotics (n, %)	1187 (*99.7*)	2115 (*99.9*)	1089 (*99.9*)	3711 (*99.9*)	2592 (*99.5*)	778 (*100*)	6200 (*98.8*)
Patients with previous operations on the knee (n, %)	311 (*26.2*)	456 (*21.6*)	333 (*30.6*)	1128 (*30.4*)	688 (*26.4*)	205 (*26.4*)	1542 (*24.6*)
Intact ACL pre-operatively (n, %)	904 (*76.0*)	1664 (*78.8*)	792 (*73.3*)	2995 (*80.7*)	1940 (*74.6*)	542 (*69.7*)	5246 (*83.6*)
Intact PCL post-operatively (n, %)	1027 (*91.9*)	1950 (*96.3*)	911 (*87.7*)	250 (*6.9*)	353 (*13.9*)	649 (*95.2*)	5941 (*97.0*)

TKR in Norway in the last decade. A sub-analysis was performed to present the risk estimates of the category of design relative to fixed modular-bearing designs.

We tested the proportional hazards assumption of the Cox model based on scaled Schoenfeld residuals.[7,8] With revision for any reason as the endpoint, the assumption was found valid for the factors 'prosthesis brand' with the Profix implant as the reference brand ($p \geq 0.1$) and 'design category' with fixed modular bearing as the reference category ($p \geq 0.6$). Bilateral TKRs were included in the study. Although this might imply a violation of the assumption of independent observations in the survival analyses, studies have shown that the impact on statistical precision is minor for both hip[9] and knee replacements.[10]

PASW Statistics v18 (IBM SPSS, Armonk, New York) and R v2.13.0 (The R Foundation for Statistical Computing, http://www.R-project.org 2008) were used for the statistical analyses, and $p < 0.05$ was considered statistically significant.

The NAR has approval from the Norwegian Data Inspectorate to collect patient data on condition of written consent of the patient.

Results

The study groups did not differ markedly with respect to age, gender, laterality or diagnosis (Table I). The median follow-up ranged from 1.8 to 6.9 years depending on the implant (Table II).

The Cox's regression analyses and the Kaplan-Meier curves showed that the Duracon, LCS Classic, LCS Complete and AGC Universal brands had a higher risk of revision (RR 1.3 to 2.6) and a statistically significantly lower survival (89.5% to 94.0%) than the Profix TKR (95.3%) (Table II, Fig. 2). The NexGen and the AGC Anatomic TKR performed in a similar manner to the Profix. A sub-analysis of TKRs performed in the latest time period, after 2004, showed a higher risk of revision for the two mobile-bearing implants (RR 1.3 (95% CI 1.0 to 1.7)), but not for monobloc implants (RR 1.0 (95% CI 0.7 to 1.4)) compared with the fixed-bearing implants.

There was an increased risk of revision for aseptic tibial loosening in the LCS Classic, LCS Complete and the Duracon TKRs compared with the Profix (RR 6.8 (95% CI CI 3.8 to 12.1), RR 7.7 (95% CI 4.1 to 14.4) and RR 4.5 (95% CI 1.8 to 11.1), respectively) (Table III and Fig. 3a). These implants also had an increased risk of revision for aseptic femoral loosening (RR 2.3 (95% CI 1.1 to 4.8), RR 3.7 (95% CI 1.6 to 8.9) and RR 3.4 (95% CI 1.1 to 11.0), respectively) (Fig. 3b). Also, the AGC Universal TKR had an increased risk of revision for aseptic tibial loosening (RR 2.5 (95% CI 1.3 to 5.1)) compared with the Profix.

The risk of revision due to deep infection was higher for all TKRs except the LCS Classic, compared with the Profix (RR from 1.8 to 3.7). The risk of revision due to polyethylene wear and to malalignment was higher in the Duracon

Table II. Kaplan-Meier survival by implant brand of cemented primary total knee replacements without patellar resurfacing, reported to the Norwegian Arthroplasty Register between 1994 and 2009, with revision for all causes as the endpoint (CI, confidence interval)

				5 years		10 years			
Implant	Total (n)	Revised (n, %)	Median follow-up (yrs)	Survival (%, 95% CI)	At risk (n)	Survival (%, 95% CI)	At risk (n)	Relative risk (95% CI)*	p-value
Profix	6276	195 (*3.1*)	4.5	96.3 (95.7 to 96.9)	2575	95.3 (94.5 to 96.1)	51	1	
Duracon	1090	56 (*5.1*)	1.8	93.3 (91.1 to 95.5)	247	89.5 (86.1 to 92.9)	117	2.6 (1.9 to 3.4)	< 0.001
NexGen	778	25 (*3.2*)	3.2	94.7 (92.5 to 96.9)	159	-†	4	1.2 (0.8 to 1.9)	0.3
LCS Classic	2606	129 (*5.0*)	6.6	95.6 (94.8 to 96.4)	1898	94.0 (92.8 to 95.2)	261	1.3 (1.0 to 1.6)	0.017
LCS Complete	3714	102 (*2.7*)	1.9	94.9 (93.5 to 96.3)	61	-‡	0	1.5 (1.1 to 1.9)	0.002
AGC Universal	2118	121 (*5.7*)	6.9	94.7 (93.7 to 95.7)	1436	92.6 (91.2 to 94.0)	369	1.6 (1.3 to 2.0)	< 0.001
AGC Anatomic	1190	29 (*2.4*)	2.7	96.5 (95.1 to 97.9)	119	-§	0	1.1 (0.7 to 1.6)	0.7

* Cox regression with adjustment for age, gender, diagnosis and previous surgery
† last revision at 4.65 years
‡ last revision at 4.31 years
§ last revision at 3.89 years

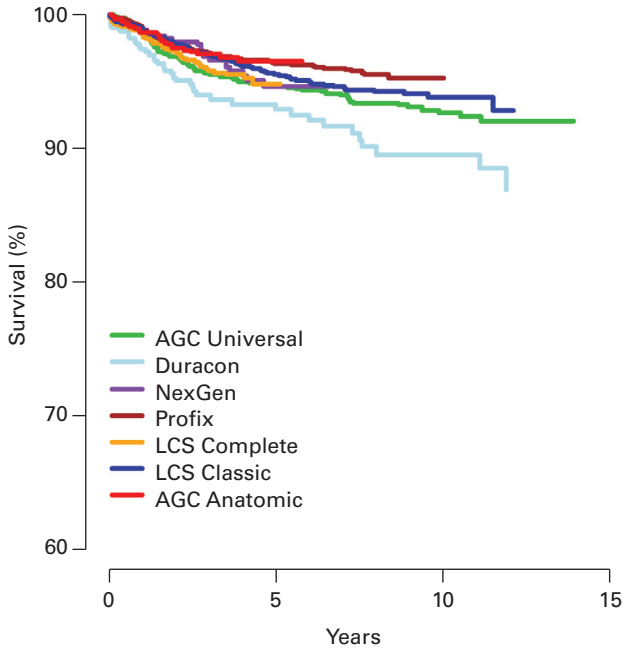

Fig. 2

Kaplan-Meier survival analysis of the various brands with revision for any reason as the endpoint.

TKRs (RR 16.6 (95% CI 4.9 to 56.7) and RR 8.7 (95% CI 3.7 to 20.4), respectively). However, the number of revisions for these reasons was low (n = 10 and n = 10, respectively). The LCS Classic had a higher risk of revision due to dislocation of the polyethylene (RR 3.7 (95% CI 1.2 to 11.1)). The AGC Universal had a higher risk of revision due to pain (RR 2.1 (95% CI 1.5 to 3.0)) and dislocation of the patella (RR 8.0 (95% CI 1.6 to 39.6)), whereas the LCS Complete and LCS Classic had a lower risk of revision due to pain as the only cause of revision (RR 0.4 (95% CI 0.2 to 0.8)). Insertion of a patellar component was the most frequent revision operation performed for pain.

Using the fixed modular-bearing category as the reference, for the three categories of design we found an increased risk of revision due to aseptic loosening of the tibial tray in the mobile-bearing (RR 4.8 (95% CI 3.2 to 7.3)) and the monobloc category (RR 1.9 (95% CI 1.1 to 3.3)). Aseptic loosening of the femoral component was more common in the mobile-bearing category (RR 2.5 (95% CI 1.4 to 4.4)). Further, we included only the most used subtypes of the implants in the analysis, but the results did not change.

In order to minimise the effect of a learning curve, we performed a sub-analysis that only included TKRs from hospitals having inserted > 100. The risk of revision for aseptic tibial loosening was still higher for the LCS Classic (RR 5.8 (95% CI 3.3 to 10.2) and the LCS Complete (RR 6.8 (95% CI 3.6 to 12.8)) compared with the Profix TKR. The type of cement did not influence survival. The mean operating time ranged from 85 minutes for the AGC Anatomic to 105 minutes for the NexGen TKR (Table I).

In order to preclude any time dependency, we analysed the one-year and five-year Kaplan-Meier overall survival rates and the Cox's regression hazard rate ratios. The differences in survival of the various brands did not change markedly over time (see Supplementary Material).

Discussion

The Duracon, LCS Classic, LCS Complete and AGC Universal brands had lower survival than the Profix, whereas the NexGen and AGC Anatomic TKRs did not. Increased risk of revision for aseptic loosening of the tibial and femoral components was the major reason for the inferior performance. The AGC Universal was more likely to be revised because of pain than the other brands, and LCS Complete and LCS Classic were less likely to be revised for this reason. The risk of revision for deep infection was higher for all brands, except the LCS Classic, than for the Profix.

The implants with a higher risk of aseptic loosening represent different design principles, so no common thread was apparent. For example, the fixed non-modular bearing AGC Universal was inferior to the Profix, but the AGC Anatomic was not.

Revision because of pain was rare with mobile-bearing implants, which is consistent with the theory that rotation of the mobile bearing improves patellar tracking.[11] The

Table III. Causes of revision by incidence and Cox's relative risk (RR) for cemented total knee replacements without patellar resurfacing reported to the Norwegian Arthroplasty Register between 1994 and 2009. There may be more than one cause of revision reported in each case. Statistically significant differences compared with the Profix implant, are marked with bold (CI, confidence interval)

	Implant						
Cause of revision	**Profix**	**Duracon**	**NexGen**	**LCS Complete**	**LCS Classic**	**AGC Universal**	**AGC Anatomic**
Incidence (n, %)							
Aseptic loosening (femur)	12 (*0.2*)	4 (*0.4*)	1 (*0.1*)	10 (*0.3*)	16 (*0.6*)	5 (*0.2*)	1 (*0.1*)
Aseptic loosening (tibia)	15 (*0.2*)	7 (*0.6*)	4 (*0.5*)	32 (*0.9*)	58 (*2.2*)	17 (*0.8*)	3 (*0.3*)
Dislocation (patella)	2 (*0.0*)	5 (*0.5*)	-	-	-	6 (*0.3*)	1 (*0.1*)
Dislocation (other)	5 (*0.1*)	-	-	1 (*0.0*)	9 (*0.3*)	1 (*0.0*)	-
Instability	31 (*0.5*)	11 (*1.0*)	5 (*0.6*)	10 (*0.3*)	13 (*0.5*)	15 (*0.7*)	5 (*0.4*)
Malalignment	12 (*0.2*)	10 (*0.9*)	2 (*0.3*)	5 (*0.1*)	13 (*0.5*)	4 (*0.2*)	2 (*0.2*)
Deep infection*	31 (*0.5*)	15 (*1.4*)	11 (*1.4*)	33 (*0.9*)	21 (*0.8*)	22 (*1.0*)	11 (*0.9*)
Fracture affecting implant	8 (*0.1*)	1 (*0.1*)	-	4 (*0.1*)	8 (*0.3*)	-	-
Pain†	68 (*1.1*)	3 (*0.3*)	3 (*0.4*)	11 (*0.3*)	14 (*0.5*)	51 (*2.4*)	7 (*0.6*)
Polyethylene wear	4 (*0.1*)	10 (*0.9*)	-	3 (*0.1*)	1 (*0.0*)	2 (*0.1*)	-
Stiffness	12 (*0.2*)	5 (*0.5*)	-	5 (*0.1*)	1 (*0.0*)	1 (*0.0*)	-
Other	27 (*0.4*)	10 (*0.9*)	1 (*0.1*)	11 (*0.3*)	7 (*0.3*)	7 (*0.3*)	-
RR (95% CI)							
Aseptic loosening (femur)	1	**3.4** (1.1 to 11.0)	0.9 (0.1 to 6.8)	**3.7** (1.6 to 8.9)	**2.3** (1.1 to 4.8)	0.8 (0.3 to 2.4)	0.8 (0.1 to 6.3)
Aseptic loosening (tibia)	1	**4.5** (1.8 to 11.1)	2.9 (0.9 to 8.6)	**7.7** (4.1 to 14.4)	**6.8** (3.8 to 12.1)	**2.5** (1.3 to 5.1)	1.7 (0.5 to 5.9)
Dislocation (patella)	1	**19.3** (3.7 to 100.3)	0	0	0	**8.0** (1.6 to 39.6)	3.1 (0.3 to 34.7)
Dislocation (other)	1	0	0	0.5 (0.1 to 4.0)	**3.7** (1.2 to 11.1)	0.5 (0.1 to 4.6)	0
Instability	1	**3.5** (1.7 to 7.0)	1.5 (0.6 to 3.8)	1.0 (0.5 to 2.1)	0.8 (0.4 to 1.6)	1.2 (0.7 to 2.3)	1.3 (0.5 to 3.3)
Malalignment	1	**8.7** (3.7 to 20.4)	1.8 (0.4 to 7.9)	1.4 (0.5 to 4.1)	2.1 (0.9 to 4.6)	0.9 (0.3 to 2.7)	1.4 (0.3 to 6.3)
Deep infection*	1	**3.7** (2.0 to 6.9)	**3.3** (1.6 to 6.5)	**2.6** (1.6 to 4.3)	1.4 (0.8 to 2.5)	**1.8** (1.1 to 3.2)	**2.4** (1.2 to 4.7)
Fracture affecting implant	1	0.8 (0.1 to 6.6)	0	1.2 (0.4 to 4.1)	1.9 (0.7 to 5.1)	0	0
Pain†	1	0.4 (0.1 to 1.4)	0.4 (0.1 to 1.3)	**0.4** (0.2 to 0.8)	**0.4** (0.2 to 0.8)	**2.1** (1.5 to 3.0)	0.7 (0.3 to 1.5)
Polyethylene wear	1	**16.6** (4.9 to 56.7)	0	4.0 (0.8 to 19.9)	0.3 (0.0 to 3.0)	0.8 (0.1 to 4.3)	0
Stiffness/Other	1	**3.7** (1.8 to 7.7)	0.3 (0.0 to 2.4)	1.1 (0.5 to 2.2)	0.6 (0.3 to 1.3)	0.8 (0.3 to 1.8)	0

* deep infection rules out aseptic loosening
† pain as the only cause of revision

AGC Anatomic, with right/left femoral components, has replaced the AGC Universal, and its good results are consistent with data from the Australian Arthroplasty Registry showing similar revision rates for monobloc and fixed-bearing TKRs after ten years.[2]

The risk of revision due to dislocation of the polyethylene bearing was higher for the LCS Classic than for the Profix, but not for the LCS Complete. In our study most of the mobile-bearing LCS TKRs sacrificed the PCL, whereas the fixed modular and fixed non-modular TKRs were PCL retaining (Table I).

This study focused on the causes of revision and found the highest risk of revision to be in the LCS TKRs, for both aseptic tibial and femoral loosening. Other studies have shown good survival and clinical results of mobile-bearing designs,[11-14] but these studies did not compare mobile with fixed bearings. The inferior results of the mobile-bearing TKRs in our study are consistent with data from the Australian Joint Replacement Registry[2] and from the Southern California Permanente Medical Group.[15,16]

The aim of the mobile-bearing design was to combine low constraint forces with low contact stresses, theoretically reducing polyethylene wear and aseptic loosening.[17] Early fixed-bearing designs had unsatisfactory function and range of movement, and it was claimed that the biomechanics of the mobile-bearing design were closer to those of a normal knee, and would improve function and longevity.[18] Dislocation of the polyethylene was a problem in the early years of the mobile-bearing TKR, but as the technique and instruments evolved, this complication became rare.[19] However, there is no strong evidence that any mobile-bearing design is superior to a fixed bearing with regard to pain, function, range of movement or failure rate.[20,21] It is claimed that wear of the polyethylene in the modular fixed bearing and the mobile bearing at the tibial interface may lead to peri-prosthetic osteolysis and loosening.[22,23] This so-called backside wear is eliminated in the fixed non-modular (monobloc) design, but the modularity option is lost. The monobloc design has excellent survival in several studies,[24-27] but most surgeons prefer the modular fixed bearing.

A retrieval study evaluating 48 mobile bearings concluded that wear was as severe as that in fixed modular-bearing designs.[28] Similar polyethylene wear was found for a mobile-bearing rotating platform and a fixed modular bearing in an *in vitro* study.[29] Another *in vitro* study, however, concluded that the wear rate of the fixed bearing was four times higher than for the rotating platform,[30] but in two meta-analyses no differences in the incidence of

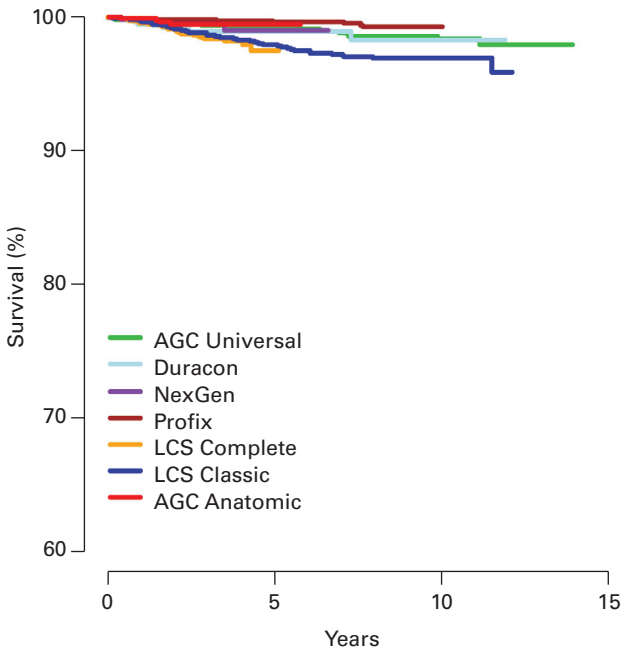

Fig. 3a

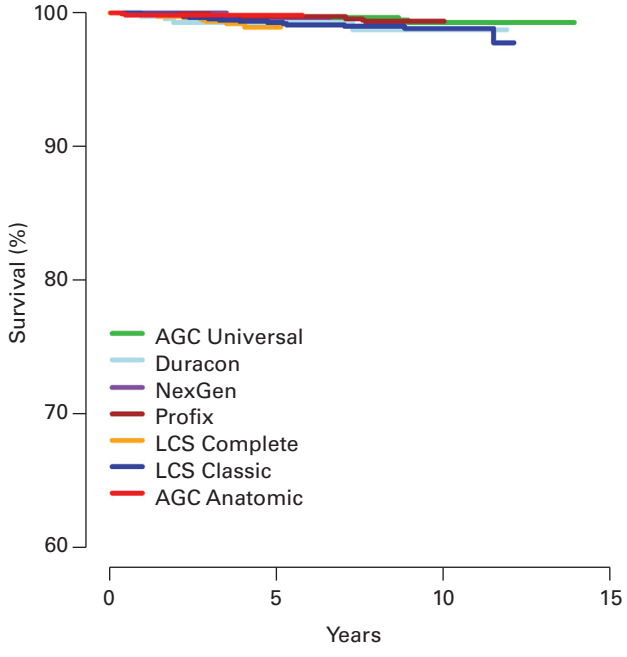

Fig. 3b

Kaplan-Meier survival analyses of the various brands with a) tibial and b) femoral loosening as the endpoint.

radiolucent lines or clinical outcome were found.[20,31] Recent reports from the NAR did not show differences in pain, function or survival for the LCS Classic, or survival for the LCS Complete, compared to the AGC Universal TKR.[32,33] Differences in geometry and undersurface texture in the two mobile-bearing TKRs might explain why they differ in outcome.[34] All the mobile-bearing TKRs in this study were 'no keel' subtypes, and there might have been less resistance to rotational forces with this design compared with those with a keel (Supplementary Material). The higher risk of revision for aseptic loosening of the tibial and femoral components in the LCS Classic and LCS Complete must be further investigated, focusing on wear and shear forces at the prosthesis–cement–bone interfaces.

The inferior results reported here for the Duracon TKR differ from those reported from the Australian Arthroplasty Register.[2] A possible explanation could be that in 2005 the Duracon TKR was introduced in one geographical region of Norway as a result of a tender process, and therefore the local surgeons were obliged to go through a learning process.

In conclusion, differences in the causes of revision were brand specific. The assumption that fixed modular-bearing implants are more at risk of loosening due to polyethylene wear than mobile-bearing designs was not supported by this study.

Supplementary material

A table detailing the use of subtypes of implants within each brand and two Kaplan-Meier survival curves showing cumulative survival at i) one and ii) five years are available with the electronic version of this article on our website www.bjj.boneandjoint.org.uk

The authors would like to thank P. J. Høl, PhD for valuable input regarding interpretation of the results. The corresponding author received funding from the Research Council of Norway.

No benefits in any form have been received or will be received from a commercial party related directly or indirectly to the subject of this article.

This article was primary edited by D. Rowley and first-proof edited by G. Scott.

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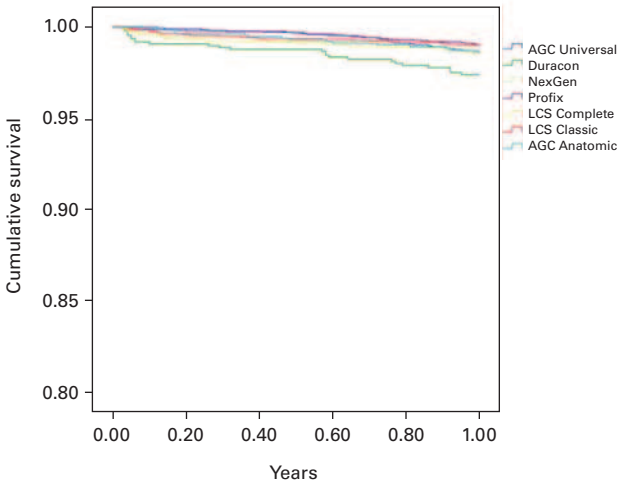
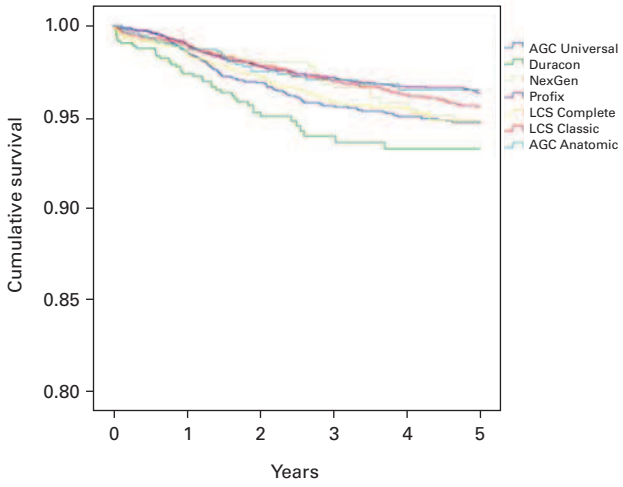


Cox's multiple regression hazard rate ratios the first year

Implant	RR (95% CI)	p-value
Profix	1	
Duracon	2.8 (1.7 to 4.5)	< 0.001
LCS Complete	1.6 (1.1 to 2.3)	0.021

Fig. i



Cox's multiple regression hazard rate ratios the first five year

Implant	RR (95% CI)	p-value
Profix	1	
AGC Universal	1.7 (1.2 to 2.0)	< 0.001
Duracon	2.3 (1.7 to 3.2)	< 0.001
LCS Complete	1.4 (1.1 to 1.8)	0.003
LCS Classic	1.3 (1.0 to 1.6)	0.042

Fig. ii

Kaplan-Meier curves showing survivorship by brand at i) one year and ii) five years, hazard rates significantly different from Profix.

Table i. Subtypes registered for each prosthesis brand and number revised

Subtype	Tibia	Femur	Revised
NexGen			
Precoat PMMA stemmed	379		8
Precoat PMMA pegged	5		1
Option	391		16
Precoat CR		31	2
Option CR		594	22
Option CRA		4	0
CR Flex Option		140	1
CR Flex gender-specific		6	0
LCS			
PCR porocoat	1		0
PCR textured	11		5
Rotating platform porocoat	7		0
Rotating platform textured	2539		128
Rev rotating platform porocoat	45		2
Mod rev	3		0
Porocoat		121	5
Textured		2474	128
Rev porocoat		3	0
Mod rev		8	0
AGC			
V2 interlok	3252		147
Interlok	61		2
Anatomic porous		2	0
Anatomic interlok		1188	29
Universal interlok		57	3
V2 interlok		2061	118
LCS Complete			
No keel MBT	3676		99
With keel MBT	1		0
MBT revision	20		1
Small, standard, large (+)		3609	94
Mod/revision-unconstrained s,m,st,l (+)		5	0
Profix			
Non-porous	6276	6276	195
Duracon			
Porous with screw fixation	4		0
Porous with stem	3		0
Porous/resurf	2		0
Cruciform/porous	110		13
Univ/porous	2		0
Univ/non-porous	9		2
Cruciform/non-porous	904		38
Bead, PCA	14		0
Resurf, PCA	36		3
Cruciform, beaded	1		0
Porous		166	14
Non-textured		780	36
Porous Modular		12	0
Non-textured Modular		121	5
Monolithic		3	0

Log no. 32516

Title: Functional outcome and alignment in computer assisted and conventionally operated total knee replacements. A multi-centre parallel-group randomised controlled trial.

Abstract:

A randomised controlled trial compared computer assisted surgery (CAS) to conventional surgery (CONV) in total knee replacement. Patients aged 55-85 years (n=192), with osteoarthritis or arthritic disease of the knee and ASA category 1-3, were recruited from 4 [Blinded] hospitals, during 2009-2011. Improvement of functional results (primary outcome) was inferior for CONV compared to CAS at 3 months follow-up; the Knee Society function score (mean difference (md) 5.9, 95% confidence interval (CI) 0.3-11.4, p=0.039), the Knee injury and osteoarthritis outcome score (KOOS) subscales for "pain" (md: 7.7, CI: 1.7-13.6, p=0.012), "sport" (md: 13.5, CI: 5.6-21.4, p=0.001) and "quality of life" (md: 7.2, CI: 0.1-14.3, p=0.046), and at 1 year follow-up; KOOS "sport" (md: 11.0, CI: 3.0-19.0, p=0.007) and "symptoms" (md: 6.7, CI: 0.5-13.0, p=0.035). CAS had fewer outliers (>3° malalignment) in frontal alignment of the entire prosthesis (37.9% vs 17.9%, p=0.042) and the tibial component (28.4% vs 6.3%, p=0.002). Tibial slope was better achieved with CAS (58.9% vs 26.3%, p<0.001). Operation time was 20 minutes longer with CAS. In conclusion, the functional results were marginally in favor of CAS. CAS was more predictable than CONV for mechanical alignment and positioning of the prosthesis. Long term effect must be further investigated.

Introduction

Total knee replacement (TKR) is well documented as beneficial in patients with knee osteoarthritis [1, 2]. However, a substantial number of patients are not satisfied with the outcome, and there is room for improvement [3]. Computer navigation has been used the last decade in total knee replacement to improve alignment and positioning of the implant. Also, this tool can help the surgeon with ligament balancing. Several authors have reported improved alignment with computer assisted

surgery (CAS) [4-6], and a recent meta-analysis of randomized controlled trials concluded that CAS does improve mechanical leg axis and component orientation in total knee replacement [7]. It remains controversial however, whether the improvement of alignment resulting from CAS gives better function [8-10] or longevity [11]. Also, there is an ongoing debate whether perfect alignment really is the target. Some argue that constitutional malalignment may not be fully corrected, and there is no hard evidence to argue against that [12]. Choong et al reported that good alignment correlated with good function [13]. They suggested this correlation was due to the use of CAS, in concordance with the dominating belief that alignment is important for good clinical results and longevity [14, 15]. However, concerning functional outcomes, the study did not compare CAS to CONV, but well-aligned against malaligned knees. To our knowledge, no trial has shown a direct correlation between the use of CAS and good functional outcome.

On this background, our aim was to perform an RCT (randomized controlled trial), where CAS was primarily evaluated against functional outcome, and secondarily against measures from CT scans and full-length standing radiographs. Our null hypothesis was that there was no difference in functional outcome between CAS and CONV. The trial was designed and conducted according to the CONSORT statement guidelines for reporting parallel group randomized trials [16].

Methods

Trial design

3a. Patients were randomly parallel-group assigned to CAS or CONV (allocation ratio 1:1).

3b. Due to a slow recruitment rate, the age criterion for inclusion was changed after 6 months from 60-80 years to 50-85 years.

4a. Eligible patients were 50-85 years old, in need of a TKR, male and female, with osteoarthritis or arthritic disease of the knee, ASA category 1-3 (The American Society of Anesthesiologists (ASA) Physical Status classification system). Exclusion criteria were severe systemic disease, severe neurological disorder, a history of cancer, dementia, body mass index > 35, previous shaft fractures of the tibia or femur, severe valgus position of the knee (> 15 degrees from the mechanical axis of

the knee), previous osteotomy of the tibia or femur, recent knee injury (less than a year preoperatively), severe stiffness of the ipsi-lateral hip, ipsi-lateral hip replacement, and allergy to metals. For patients in need of two knee replacements, only the knee first evaluated in the recruitment period was included in the trial.

4b. Recruitment period was 2009-2011, and patients were recruited from orthopaedic clinics at four hospitals in [Blinded]. Eight surgeons performed the knee replacements. They were all experienced in TKR (performed > 100 CONVs), and each surgeon had done at least 10 TKRs with the use of CAS before recruiting patients into the trial.

5. A cemented Profix total knee prosthesis (Smith & Nephew) was implanted in all patients (Figure 1), using Palacos R+G cement (Heraeus, Hanau, Germany). Of the two dominating techniques in TKR, "measured bone resection" and "gap balancing", [17, 18], we chose to perform the "measured bone resection" technique in all cases to equalize the groups. The principles of TKR taught by Leo Whiteside were applied [19]. No patella resurfacing was performed. The tibial component was implanted with the aim of a 4 degrees posterior slope. In the CONV group traditional instruments and intramedullary rods were used, and the femoral component was inserted in a neutral alignment in the frontal plane (referring to the mechanical axis, surgeon could choose between 5° and 7° cutting blocks with reference to the intramedullary rod) and the sagittal plane (referring to the anatomical axis), or optionally with a 4 degrees flexion of the femoral component. In the CAS group, a neutral alignment was aimed for in the frontal plane, and an individualized flexion of the femoral component was allowed in the sagittal plane. Two 4 millimeter bi-cortical pins were drilled into the femur and tibia to affix the reflection beads. The pins into the femur were placed inside the main incision, but the pins into the tibia were placed distal to the main incision with two minor stab incisions. The CAS technology used was the VectorVision knee software version 1.6.93616, with the Kolibri system from BrainLAB, Munig, Germany. All patients started weight bearing and standardized exercises the first postoperative day. Tranexamic acid 10 mg/kg was administered intravenously 10 minutes before surgery, and was repeated 10 minutes before release of the

tourniquet. No drains were applied to the operated knee, and the knee was positioned in a supine figure of four (90 flexion of the operated knee) for two hours, to minimize bleeding. Antithrombotic medication was administered 4 hours postoperatively and once daily for 17 days (40 mg enoxaparin for subcutaneous injection). Antibiotic medication was administered intravenously within 30 minutes before surgery, after 4 hours, 8 hours and 12 hours, as a prophylaxis against infection (cephalotin 2 g x 4). The skin incision was closed with agraffes.

6a. Primary outcome was functional scores (Knee Society Score (KSS), Knee injury and Osteoarthritis Outcome Score (KOOS), EQ-5D and Visual Analogue Scale (VAS)) after 3months and 1 year. The VAS was a sheet with a100 millimeters long line ranging from 0 (no pain) to 1 (worst thinkable pain), on which the patients were asked to mark their worst knee pain experience during the last week before assessment. Secondary outcomes were alignment and rotational positioning of the implant. CT scans were performed 3 months after surgery (Figure 2 a/b). In addition, full-length radiographs were performed preoperatively and 3 months after surgery (Figure 3). Frontal alignment of the operated limb was measured on full-length radiographs as the angle formed by the centres of the hip, knee and ankle. For CT-scans this outcome was the sum of the frontal alignments of the femoral component and the tibial component. The radiographic measures were performed by 4 specially trained assistants (1 nurse, 1 medical student and 2 radiologists) according to a specific protocol (Appendix). Functional scores were carried out by 8 physical therapists at the 4 institutions before the operation, after one week (only Range Of Motion (ROM) and VAS), after 3 months and after 1 year. Physical therapists were pre-instructed how to score the patients in the clinical evaluation part of the KSS. A long-armed goniometer was utilized, and the anatomical landmarks used, were the most prominent parts of the greater trochanter, the lateral epicondyle, and the lateral malleolus. ROM was defined as extension lag (degrees of active extension deficit) subtracted from maximum active flexion.

7a. To reveal a difference of 10 units in KOOS [20] with a standard deviation of 20, a sample size of 64 patients per group was necessary to achieve a power of 80% and a 5% significance level. Alignment in the frontal plane was a secondary outcome, and we calculated statistical power to reveal an average difference across the groups of 0.5°. According to previous studies we assumed greater variation of measures in the CONV group (standard deviation (sd) = 1.3) than in the CAS group (sd = 0.9) [4]. With a two-sided 5% significance level and a power of 80%, a sample size of 79 patients per group was necessary. A total of 204 patients were included. A pilot study of 12 patients was determined from the start of the recruitment not to be included in the final study population.

8a. Separate randomization lists were created for each of the 8 surgeons using the statistical software PASW Statistics v 19 (IBM SPSS, Armonk, New York).

8b. Block randomization with randomly varying block sizes of 2 and 4 was generated to achieve approximate equal numbers in the treatment groups at all times.

9. A central randomization office performed computer-generated allocation to trial group, with concealment by identical, opaque, sequentially numbered, sealed envelopes.

10. An investigator with no clinical involvement in the trial performed the randomization, and sequentially numbered envelopes were sent to an independent local contact. After the surgeon had obtained the patient's consent, the independent local contact was contacted for allocation assignment.

11. Patients, nurses, physical therapists, research assistants and outcome assessors were blinded to group assignment. The blinding procedure involved two stab incisions for the CONV patients, at the same location as the stab incisions with CAS. The computer navigation equipment was present and switched on during every operation to blind the patient. The person measuring the angles on CT scans and radiographs was initially blinded, but sometimes the holes in the tibia and femur, made by the fixator pins, were revealed on the images being measured.

12. To compare mean angles, means and mean improvements of the KSS, KOOS, EQ-5D and VAS, we used independent samples t-tests with 95% confidence intervals. Differences in outliers, age,

Charnley category, sex, side and diagnosis were assessed by the Pearson Chi-square test. All tests were two-sided. P-values > 0.05 were considered statistically significant. The software package IBM SPSS Statistics 20, was used in all analyses and calculations. The correlation of radiological measurements performed by different assistants was assessed by Intraclass Correlation Coefficient (ICC2), [21].

Ethics

The trial was approved by the Regional committee for medical and health research ethics, [Blinded] September 29, 2007 (ref.no:2007/12587-ARS).

13. Results

13a/b. 192 patients aged 55-85 were included in the trial, randomly allocated to CAS (n=97) and CONV (n=95). All analyses were performed according to the principle of intention to treat. The functional outcome analyses involved 92 (CAS) and 90 (CONV) patients at 3 months follow-up, and 88 (CAS) and 87 (CONV) patients at one year follow-up. The radiological analyses involved 95 patients in the CAS group and 94 patients in the CONV group (Figure 4).

14a. Patients were recruited from May 2009 until August 2011.

15. The CAS group and the CONV group did not differ with respect to age, sex or side of operation (Table 1). Preoperatively 2/3 of the patients had a varus position and 1/3 a valgus position of the knee, equally distributed among the groups. There were a few more patients within Charnley category 3 (multiple joint disease or other disease affecting the ability to walk) in the CONV group (7.4% vs 1.1%, but the difference was not statistically significant, p=0.083).

16. Due to logistic problems at one hospital, there were some drop-outs from the functional scoring at 1 year (Table 2a/b).

17a. (Table 2a/b).

The improvement in the Knee Society function score and the KOOS subscales for “pain”, “sport” and “quality of life”, were statistically significantly better in the CAS group than in the CONV group at 3 months; Knee Society function score (mean difference (md) 5.9, 95% confidence interval (CI) 0.3 to 11.4, p=0.039), the Knee injury and osteoarthritis outcome score (KOOS) subscales for “pain” (md: 7.7, CI: 1.7 to 13.6, p=0.012), “sports” (md: 13.5, CI: 5.6 to 21.4, p=0.001) and “quality of life” (md: 7.2, CI: 0.1 to 14.3, p=0.046). After 1 year the KOOS “quality of life” and “pain” subscales were no longer better in the CAS group, but the improvement of the KOOS subscale for “symptoms” was now better in the CAS group (md: 6.7, CI: 0.5 to 13.0, p=0.035), and the superiority in “sports” prevailed (md: 11.0, CI: 3.0 to 19.0, p=0.007).[20]. There were no statistically significant differences detected between the groups with regard to improvement of VAS or EQ-5D. For all scores the crude mean values were better in the CAS group at 3 months and 1 year follow-up, but the differences are small and most of them are not statistically significant. Blood loss was similar in the two groups. Operating time was 20 minutes longer in the CAS group.

17b. At 3 months follow-up, we detected more outliers in the CONV group for the HKA (“Chi 1”, 37.9% vs 17.9%, p=0.042) (Figure 5), the tibial component frontal plane position (“Beta 1”, 28.4% vs 6.3%, p=0.002), and the tibial slope (defined as outside 86 ± 3 degrees (58,9% vs 26.3%, p<0.001)). For the other angles measured there were no significant differences in outliers between the two groups. The mean angles of the frontal plane and the tibial slope were statistically significantly closer to the target in the CAS group (Table 3a). Mean angle measurements and outliers on full-length radiographs in the frontal plane (“Chi 2, Alfa 2, Beta 2”) were similar to those on the CT scans. However, fewer outliers were detected on radiographs than on CT scans (Table 3a/b).

18. Subanalysis

An inter- and intraobserver analysis (ICC2) of the CT scans measures, with a two-way mixed effect model, showed good correlation using an absolute agreement definition for single measures (Table 3a).

19. Complications

Complications were evenly distributed between the two groups (Table 4). Infection was the cause of revision in 3 cases. Two of them were treated with a two stage revision operation, and one with debridement and exchange of the polyethylene component. One of the patients (CONV group) with at two stage revision operation recovered and is now functioning well with his revision prosthesis. The other one (CAS group) did not recover well and had to amputate his femur. He has now recovered from the infection. The patient having a debridement and exchange of polyethylene (CONV group) recovered well from the infection. A suspected superficial infection was found in 2 patients. One of them was treated with oral antibiotics and no further treatment was necessary (CONV group). The other one got a chronic wound were one of the fixator pins had been placed, and it was treated by a limited excision of the wound (CAS group). Arthrofibrosis was the cause of revision in 1 patient (CONV group). In the CAS group, 1 patient got a femoral fracture which was managed with open reduction and internal fixation with an anatomic locking plate. Another patient got a minor, intraoperative fissure in the medial tibial plateau, which was ignored and healed well (CONV group). After a fall due to inebriation, 1 patient got a minimally displaced fracture of the medial tibial condyle. He was treated with a plaster splint for 3 weeks and further with an articulated knee orthosis for another 6 weeks. He recovered well (CONV group). Another patient presented symptoms from the ipsilateral hip a month after the operation and was diagnosed with a femoral head necrosis (CAS group). He got at total hip replacement 4 months after his TKR. Decubital wounds on both heels were found in 1 patient postoperatively (CAS group). They healed with no further complications. Manual mobilization of the knee under general anaesthesia, was performed in 6 knees within 3 months postoperatively, because of stiffness (4 in the CONV group and 2 in the CAS group). A transient atrial fibrillation was detected in 2 patients (1 in the CAS

group and 1 in the CONV group). Bilateral, perihilar lung embolism occurred in 1 patient (CONV group). He was treated with warfarin for 6 months and recovered completely.

Discussion

Some functional scores were marginally better with CAS compared to CONV, at 3 months and 1 year follow-up. The clinical significance of this marginal improvement is uncertain. CAS seems to be a more precise method than the CONV when performing TKR. We found fewer outliers in the CAS group for alignment of the hip-knee-ankle angle, and for the tibial slope. The improved positioning may have an impact on implant survivorship in the long term. However, CAS is time consuming.

Strength and limitations:

To our knowledge, this is the largest CT controlled randomized trial performed on these topics. This multi-centre study involved 8 surgeons from 4 institutions, providing good external validity of the results.

A multi-centre study, with multiple surgeons involved, may be weakened by differences regarding surgical procedures, unequal experience and skills, selection of patients suitable for surgery, a large number of clinical evaluators, different rehabilitation programs and different evaluating tools/procedures (subtypes of CT scanners, radiographs, goniometres). Thorough preparations were done prior to the study in order to balance the differences. Other navigation systems and other implants may have different results.

Explanations/mechanisms:

Our trial investigated the relationship between functional results and the use of computer navigation in total knee replacement, as the primary outcome. Secondary outcomes were alignment and positioning of the implant achieved by the two techniques. The functional results of well aligned

and malaligned knees must not be confused with the results of computer navigation and conventional technique, and we agree with Harvie et al, that those data should be dealt with separately [22]. There could be reasons other than good alignment, explaining the functional results of navigated knees. Indeed, CAS allows the surgeon to perform an accurate ligament balancing, the sizing of implant components might be different, and tissue insult might be less extensive.

Comparison with other studies:

In a large CT controlled trial by Kim et al, both knees were replaced sequentially under one anesthesia, by one experienced surgeon, using CAS in one knee and CONV in the other knee [23]. Two different implant designs were used. The navigation system was similar to the one used in our trial. No differences were found regarding alignment, function or mid-term survivorship.

Our trial involved 8 surgeons with unequal experience, thus giving a better external validity. When performing sequential operations under the same anaesthesia, there might be a transfer of information from the computer navigated knee to the conventionally operated knee, guiding the surgeon. However, this is not the normal situation for most surgeons performing TKRs. The excellent results by Kim et al might show that great experience with both methods and a sequential operation under the same anesthesia omits the need for a more precise instrument like CAS. The trial by Chauhan et al. was stopped for ethical reasons when the authors, in an interim analysis, found a better improvement of alignment with CAS. The 2 year and 5 year functional results have been published later, but the results were similar in the groups [22, 24]. However, the numbers were too low to conclude according to our power calculations. Only 60 patients were assessable, 30 in each group. Our power calculations suggested at least 64 patients in each group in order to reveal a difference in KOOS score of clinical relevance (> 10 points on any subscale).

In most studies on CAS and alignment, the definition of malalignment is based on the early assumptions of Jeffrey et al in 1991, suggesting that good survivorship was related to alignment within 3 degrees of mechanical axis [25]. The assumption has been questioned by others, and other

values have been suggested [26]. In lack of clear definitions, we accepted 3 degrees as the limit value of good alignment.

Good alignment is probably not the only factor leading to good longevity. A recent study from the Norwegian Arthroplasty Register reported inferior short term survivorship for certain implant brands when CAS was used [27]. The results of CAS may be affected by the implant and the navigation system being used, as well as surgical training programs and learning curves.

The operation time was prolonged by 20 minutes with CAS in the present trial. For some centres the prolongation may imply fewer operations per day and reduced cost-effectiveness.

Conclusion

Some functional scores are statistically significantly better with CAS, but for the patient this effect is marginal and probably sub-clinical in the short term. CAS is more predictable than conventional TKR, when aiming at mechanical alignment of the limb. The effect on implant survivorship and cost-effectiveness must be further investigated.

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Table 1. Demographic data and preoperative features of the patients			
	CAS[a]	CONV[b]	
n	95	94	
Men, n (%)	37 (40.2)	35 (38.0)	
Mean age (years)	68.3 (SD 7.8)	67.7 (SD 6.8)	
Right side, n (%)	56 (60.2)	57 (60.6)	
Charnley category, n (%) 1 2 3	 31 (33.0) 62 (66.0) 1 (1.1)	 33 (35.1) 54 (57.4) 7 (7.4)	
Diagnosis[c] Osteoarthritis Other	 83 (89.2) 10 (10.8)	 78 (83.9) 15 (16.1)	
Preop HKA[d]	182.2 (SD 7.2)	182.7 (SD 6.8))	
Preop valgus, n (%)	28 (32.9)	28 (32.2)	
Preop varus, n (%)	57 (67.1)	59 (67.8)	
Preop HKA missing n (%)	10 (10.5)	7 (7.4)	
[a]CAS=Computer Assisted Surgery, [b]CONV=conventional technique, [c]Percentage, [d]HKA=Hip Knee Ankle angle (crude mean value measured on radiographs)			

Table 2a. Independent samles t-test comparing CAS and CONV with respect to differences between preoperative scores and scores at 3 months follow-up (Δ3m), and between preoperative scores and scores at 1 year follow-up (Δ1y)					
	CONV	CAS	Mean difference (95% CI)	p-value	Number analyzed (n) CAS/CONV
Δ3m KSSfunc	5.6	11.5	5.9 (0.3-11.4)	**0.039**	92/90
Δ1y KSSfunc	20.7	23.6	2.9 (-2.5-8.3)	0.290	88/87
Δ3m KSSsc	8.3	12.6	4.3 (-1.9-10.4)	0.173	92/90
Δ1y KSSsc	22.7	26.4	3.8 (-2.2-9.8)	0.214	88/87
Δ3m ROM	-17.2	-12.5	4.6 (-0.7-10.0)	0.090	92/89
Δ1y ROM	-4.9	-2.3	2.5 (-2.6-7.7)	0.328	88/87
Δ3m KOOS					
Pain	19.7	27.4	7.7 (1.7-13.6)	**0.012**	91/90
Symptoms	7.0	13.1	6.0 (-0.4-12.5)	0.066	92/90
Activity of daily living	20.9	26.3	5.4 (-0.06-10.9)	0.052	92/89
Sport	7.6	21.1	13.5 (5.6-21.4)	**0.001**	87/84
Quality of life	27.8	35.0	7.2 (0.1-14.3)	**0.046**	91/89
Δ1y KOOS					
Pain	34.3	39.8	5.5 (-1.0-12.0)	0.096	87/86
Symptoms	21.6	28.3	6.7 (0.5-13.0)	**0.035**	88/87
Activity of daily living	30.5	34.8	4.3 (-1.6-10.1)	0.153	85/87
Sport	23.6	34.6	11.0 (3.0-19.0)	**0.007**	84/85
Quality of life	41.5	48.6	7.1 (0.0-14.3)	0.052	88/87
Δ3m EQ-5D	14.7	19.3	4.7 (-1.7-11.0)	0.151	86/85
Δ1y EQ-5D	23.8	29.4	5.6 (-1.3-12.6)	0.111	83/85
Δ3m VAS	35.5	41.6	6.2 (-1.9-14.3)	0.133	88/89
Δ1y VAS	45.6	53.4	7.8 (0.0-15.7)	0.051	83/83

Table 2b. Independent samples t-test comparing crude mean values of CONV[a] vs CAS[b] with respect to ROM[c], KSS[d], KOOS[e], EQ-5D[f], VAS[g], Hemoglobin drop, number of patients in need of transfusions and operating time.

	CONV	CAS	Mean difference (95% CI)	p-value	Numbers analysed (n), CAS/CONV
ROM preop (degrees, 95% CI)	110.4	109.1	1.3 (-3.7-6.2)	0.609	93/94
ROM postop (degrees, 95% CI)	65.2	66.0	0.8 (-3.2-4.8)	0.696	92/91
ROM 3months (degrees, 95% CI)	93.2	96.7	3.4 (-0.5-7.3)	0.084	92/89
ROM 1 year (degrees, 95% CI)	105.7	106.7	1.1 (-2.4-4.6)	0.550	88/87
Knee score preop	41.2	38.3	2.9 (-7.4-1.6)	0.205	93/94
Knee score 3 months	49.2	50.9	1.6 (-3.2-6.5)	0.510	92/90
Knee score 1 year	63.8	65.1	1.3 (-3.6-6.2)	0.610	88/87
Function score preop	59.1	60.8	1.7 (-2.9-6.3)	0.479	93/94
Function score 3 months	64.9	72.3	7.4 (1.8-13.1)	**0.009**	92/90
Function score 1 year	79.6	84.1	4.5 (-0.7-9.7)	0.092	88/87
KOOS 3 months					
Pain	65.7	72.2	6.5 (1.3-11.6)	**0.014**	91/90
Symptoms	61.8	65.9	4.0 (-1.1-9.2)	0.124	92/90
Activity of daily living	71.4	75.2	3.8 (-1.0-8.5)	0.117	92/89
Sport	23.6	33.5	9.9 (3.0-16.9)	**0.005**	87/85
Quality of life	54.3	59.7	5.4 (-0.8-11.6)	0.088	91/89
KOOS 1 year					
Pain	80.1	83.8	3.7 (-2.1-9.4)	0.209	87/86
Symptoms	76.4	80.8	4.4 (-0.3-9.1)	0.067	88/87
Activity of daily living	80.4	83.4	3.0 (-2.3-8.3)	0.263	85/87
Sport	39.7	46.8	7.1 (-0.8-14.9)	0.077	84/85
Quality of life	67.8	73.1	5.3 (-1.3-11.8)	0.115	88/87
EQ-5D 3 months	72.3	76.3	4.0 (-0.9-8.9)	0.109	88/86
EQ-5D 1 year	81.4	84.2	2.9 (-2.9-8.6)	0.325	85/86
VAS 3 months	29.6	23.6	6.0 (-0.6-12.6)	0.074	89/90
VAS 1 year	19.4	11.9	7.5 (1.2-13.8)	**0.019**	84/84

Drop in S-Hemoglobin (95%CI)	2.6	2.5	0.1 (-0.2-0.4)	0.380	88/89
Blood loss women (ml)	893	829	63 (-126-253)	0.508	42/44
Blood loss men (ml)	1215	1033	182 (-68-432)	0.150	27/30
Blood transfusions (number of patients)	4	4			
Operating time (minutes)	86.0 (81.5-90.5)	106.3 (102.7-109.9)		**<0.001**	

[a] CONV – conventional technique, [b] CAS – Computer Assisted Surgery, [c] ROM – Range of Motion, [d] KSS – Knee Society Score, [e]KOOS – Knee injury and osteoarthritis outcome score, [f]EQ-5D – quality of life score from the EuroQol group, [g]VAS – Visual Analogue Scale, [h]Blood loss formula based on serum pre- and postoperative haematocrit values, sex, height and weight

Table 3a. Angles and outliers[a] in the CAS[b] vs the CONV[c] group, measured by CT scan[d] at 3 months										
CT scan		CAS (n=95)		CONV (n=94)						
	Angle measured	Mean (SD[e])	Outliers (%)	Mean (SD)	Outliers (%)	md[f] (95% Confidence interval)	Independent samples t-test comparing means, p-value	Chi-square test comparing outliers, p-value	Inter-class correlation coefficient[g]	Intra-class correlation coefficient[g]
	Alfa 1	89.0	13.7	90.0	18.9	1.0 (0.4-1.6)	**0.001**	0.881	0.93	0.92
	Beta 1	91.1	6.3	91.8	28.4	0.8 (0.3-1.2)	**0.001**	**0.002**	0.82	0.75
	Gamma 1	87.9	48.4	88.6	32.6	0.7 (-0.4-1.7)	0.204	0.226	0.90	0.83
	Sigma 1	87.6	26.3	89.3	58.9	1.8 (1.0-2.5)	**<0.001**	**<0.001**	0.85	0.91
	Lambda 1	91.2	27.4	91.3	44.2	0.1 (-0.8-1.0)	0.858	0.165	0.69	0.80
	Mu 1	78.8	53.7	79.0	67.4	0.1 (-1.6-1.9)	0.872	0.252	0.70	0.90
	Omega 1	1.1	36.5	1.3	34.7	0.3 (-0.6-1.1)	0.536	0.970	0.85	0.93
	Chi 1	180.0	17.9	181.8	37.9	1.8 (1.1-2.5)	**<0.001**	**0.042**		

[a]outliers: alignment is deviating ≥ 3 degrees from the target,
[b]CAS=Computer Assisted Surgery, [c]CONV=Conventional technique, [d]CT scan= Computer Tomography scan, [e]SD=standard deviation,
[f]md=mean difference, [g]Two-way mixed effect model using absolute agreement for single measures definition

Table 3b. Angles and outliers[a] in the CAS[b] vs the CONV[c] group, measured by full-length radiographs at 3 months								
Radiograph		CAS (n=95)		CONV (n=92)				
	Angle measured	Mean (SD[d])	Outliers (%)	Mean (SD)	Outliers (%)	md[e] (95% confidence interval)	Independent samples t-test comparing means, p-value	Chi-square test comparing outliers, p-value
	Alfa 2	89.2	11.5	90.0	15.8	0.8 (0.2-1.4)	**0.010**	0.384
	Beta 2	90.9	18.8	91.9	34.7	1.0 (0.4-1.6)	**0.001**	**0.020**
	Chi 2	180.1	26.0	182.0	38.9	1.9 (1.0-2.7)	**<0.001**	0.077
[a]Outliers: Alignment is deviating ≥ 3 degrees from the target, [b]CAS=Computer Assisted Surgery, [c]CONV=Conventional technique, [d]SD=standard deviation, [e]md=mean difference								

Table 4. Complications. Number of cases for each treatment group.		
	CONV[a]	**CAS[b]**
Deep infection	2	1
Superficial infection	1	1
Arthrofibrosis	1	
Femoral fracture		1
Tibial fracture	2	
Lung embolism	1	
Paroxystic atrial fibrillation	1	1
Necrosis of femoral head		1
Decubitus heels		1
Technical errors with the computer		2
Stiffness of the knee calling for mobilization under general anaesthesia	4	2
Total	12	10
[a]CONV=Conventional technique, [b]CAS=Computer Assisted Surgery		

Reference List

(1) Chauhan SK, Clark GW, Lloyd S, Scott RG, Breidahl W, Sikorski JM. Computer-assisted total knee replacement. A controlled cadaver study using a multi-parameter quantitative CT assessment of alignment (the Perth CT Protocol). J Bone Joint Surg Br 2004; 86(6):818-823.

(2) Matziolis G, Krocker D, Weiss U, Tohtz S, Perka C. A prospective, randomized study of computer-assisted and conventional total knee arthroplasty. Three-dimensional evaluation of implant alignment and rotation. J Bone Joint Surg Am 2007; 89(2):236-243.

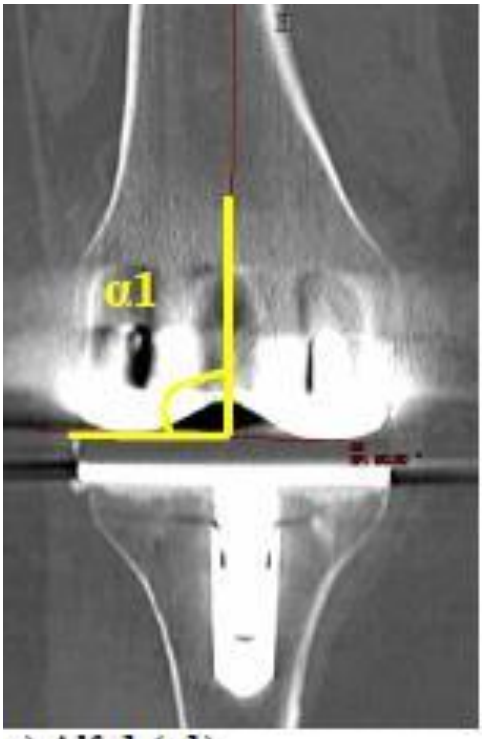
(3) Paley D, Herzenberg JE, Tetsworth K, McKie J, Bhave A. Deformity planning for frontal and sagittal plane corrective osteotomies. Orthop Clin North Am 1994; 25(3):425-465.

(4) Paley D, Pfeil J. [Principles of deformity correction around the knee]. Orthopade 2000; 29(1):18-38.

(5) Moreland JR, Bassett LW, Hanker GJ. Radiographic analysis of the axial alignment of the lower extremity. J Bone Joint Surg Am 1987; 69(5):745-749.

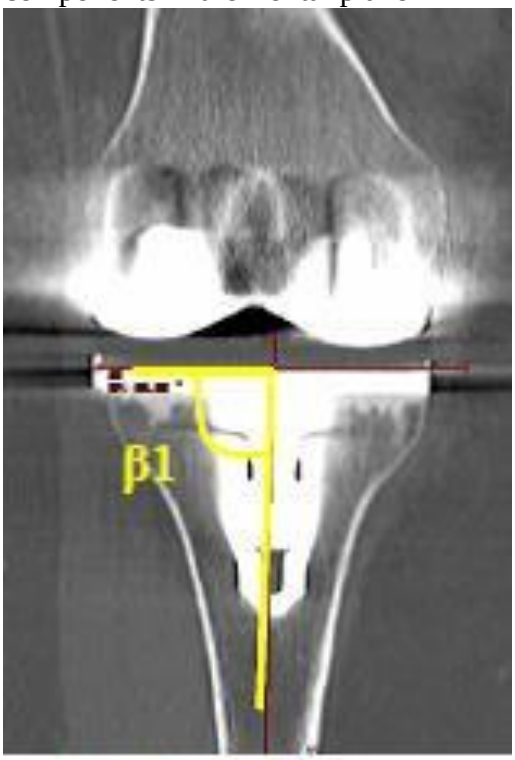
(6) The influence of femoral component position and tibial posterior slope on knee stability and range of motion after total knee arthroplasty. 70th Annual Meeting American Academy of Orthopaedic Surgeons; 03 Feb 13; 2003.

Figure 1: The Profix knee from Smith & Nephew, non-porous for cementation, with keel stem, no patella resurfacing.



a) Alfa1 (α1)

Figure 2a: Figure 2 a/b. CT scan showing the alignment of the femoral (a) and tibial (b) components in the frontal plane



b) Beta1 (β)

Figure 2b: See Figure 2a

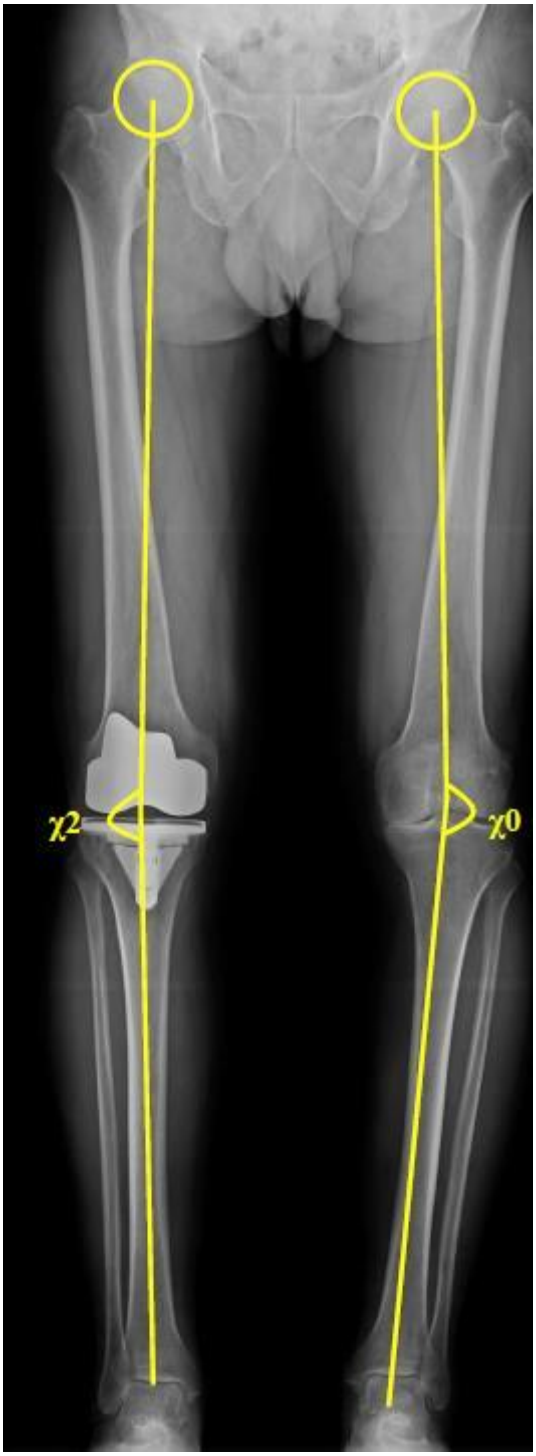


Figure 3: The Hip-Knee-Ankle angle on full-length radiographs of a prosthetic knee (chi 2) and a non-operated/native knee (chi 0)

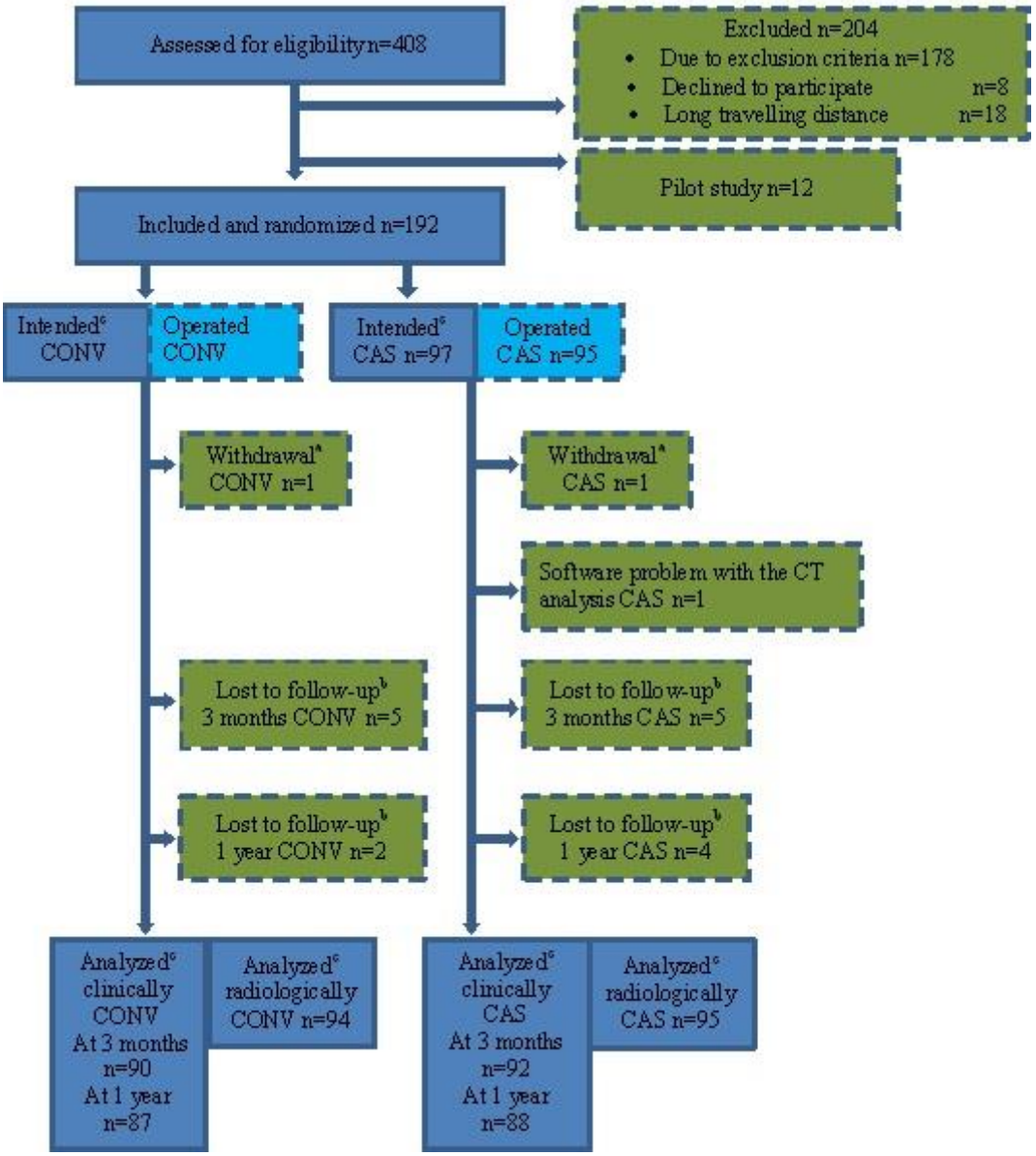


Figure 4: Flow chart illustrating patient selection for the trial. a)One patient in the CONV group changed his mind after inclusion and refused to participate. One patient in the CAS group did not want to continue his participation in the trial due to long travelling distance from his home to the hospital. b)Logistical problems due to sick-leave of a research assistant . c)Analyzed as intention to treat.Two patients were converted from CAS to CONV due to technical problems with CAS.

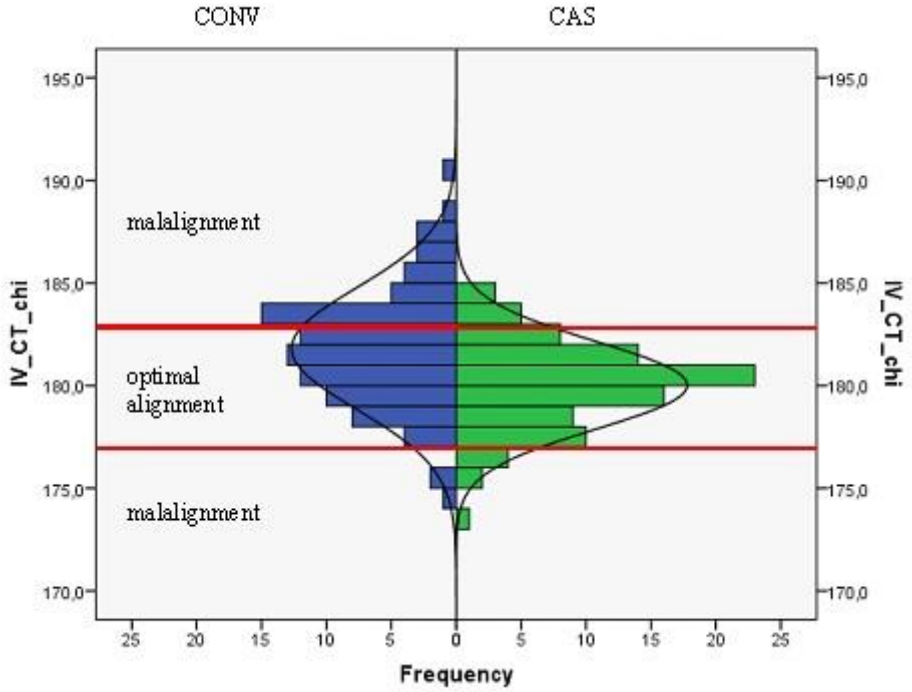


Figure 5: Outliers for Hip-Knee-Ankle angle (Chi 1), defined as <177 degrees or >183 degrees

APPENDIX

Protocol - alignment and position

All angles are measured from the lateral side (coronal (frontal) view) or posteriorly (sagittal view).
All images in this protocol are from a right side knee.

Part 1. Computer tomography scans
Part 2. Full-length standing radiographs

Part 1. Computer tomography scans – method and definitions

Timing:
Performed at 3 months follow-up

Equipment:
A multi-slice scanner (64 slices) was used at 3 months follow-up at all hospitals involved in the trial, and the tomography was performed according to the Perth protocol [28].
Software for measurements of alignment: IMPAX Agfa version 6.4.0.4551. The images are analyzed using two computer screens facilitating cross-bearing in three dimensions, and data are registered directly into the database.

Positioning:

Patient in a supine position with toes pointing towards the roof. Ankles placed in a neutral position. Forefeet supported by taping/support if needed, to avoid outward rotation of the legs.

Definitions:

Mechanical axes of the knee replaced limb[29-31]:
Femur - coronal view: Axis from centre of hip to centre of femoral component
Femur - sagittal view: Axis from centre of hip to rotational centre of femoral component
Tibia - coronal and sagittal view: Axis from centre of tibial component to centre of ankle
Limb - coronal view: Femoral axis + Tibial axis

Centre of joints:
General principle: cross-bearing in three dimensions (Fig.A)

Hip:
Draw a circle to find centre of the femoral head (Fig.A1/A4)

Knee/Femoral component:
Coronal view: Point (on the joint line) where a perpendicular of the condylar tangent points towards the deepest part of the intercondylar groove (Fig.A2).
Sagittal view: Point (on the joint line) where a perpendicular of the condylar tangent points towards the deepest part of the intercondylar groove (Fig.A3).
Axial view: Mid-point of a line between the anterior faces of the pegs (Fig A8).

Centre of rotation/sagittal view: Draw circles to find a) the centre of the anterior part of the medial condyle, and b) the centre of the posterior part of the medial condyle (a typical J-shaped articulation). Centre of rotation of the knee is defined as the mid-point between these centres.(Fig.B)

Knee/Tibial component:
Coronal view: Mid-point of longest line from lateral to medial (Fig.C1).
Sagittal view: A line parallel and posterior to the stem crosses the upper surface of the tibial component. This crossing is defined as centre of the tibial component (Fig.C2).
Axial view: Mid-point of longest line from lateral to medial, crossing the centres of two oval shaped joint surfaces of the tibial component (Fig.C3).

Ankle (Fig.D):
Coronal view:
Middle of the ankle is defined as the mid-point of a line on the talus from medial to lateral.
Sagittal view:
Mid-point of the talar dome. (If the ankle is plantarly flexed, use the mid-point of the distal tibial joint surface)
Axial view:
Mid-point of a line from medial to lateral talar body.

Measures: Alignment and position of the implant:

1. Alfa1 (α1, Fig.E1): Alignment of the femoral component in the coronal view, referring to the mechanical axis of the "new" femur.
    a. The line between the pegs, adjusted with the tangent of the condyles, defines the line of the implant. This line is measured against the mechanical axis of the femur.
2. Beta1 (β1, Fig.E2): Alignment of the tibial component in the coronal view, referring to the mechanical axis of the "new" tibia.
    a. A line parallel to the upper surface of the tibial component, adjusted with a perpendicular line parallel to the stem, defines the line of the implant. This line is measured against the mechanical axis of the tibia.
3. Gamma (γ, Fig.E3): Alignment of the femoral component in the sagittal view, referring to the mechanical axis of the "new" femur.
    a. The mechanical axis in the sagittal plane is defined as the axis from the centre of the hip to the rotational centre of the femoral component. A line drawn parallel to the pegs adjusted by any of the backsides of the femoral component, defines the line of the implant. This line is measured against the mechanical axis of the femur.
4. Sigma (σ, Fig.E4): Alignment of the tibial component in the sagittal view, referring to the mechanical axis of the "new" tibia.
    a. A line parallel to the upper surface of the tibial component, adjusted with a perpendicular line parallel to the stem, defines the line of the implant. This line is measured against the mechanical axis of the tibia.
5. Lambda (λ, Fig.E5): The rotational position of the femoral component relative to the trans-epicondylar line. A line parallel to the posterior condyles, adjusted by a line between the pegs, defines the line of the implant. The perpendicular of this line is

measured against the trans-epicondylar axis. The trans-epicondylar axis is drawn from the most prominent part of the lateral epicondyle to the deepest point of the groove between the insertion of the superficial and the deep medial collateral ligament. (In cases with no groove, the most prominent part of the medial epicondyle is chosen as the reference point).

6. Mu (μ, Fig.E6): The rotational position of the tibial component relative to the anterior posterior axis (AP-axis). A line parallel to the posterior condyles defines the line of the implant. The AP- axis is defined as a line drawn from a point marking 1/3 of the medial tibial tubercle to a point representing the insertion of the posterior cruciate ligament. A CT slice where an S-shape is found at the back of the tibia is chosen, and the posterior point is marked where the concavity of the S turns into convexity.
7. Omega (ω, Fig.E7): The line of the femoral component in Lambda (λ) is superimposed on the line of the tibial component in Mu (μ). The angle between the two components represent a match/mismatch. Ideally this angle should be 10°, since the tibial component of the Profix prosthesis is supposed to be positioned in 10° internal rotation to achieve good bone coverage. (The polyethylene joint surface is externally rotated 10° to neutralize the rotation of the tibial component. Then the match between the polyethylene joint surface and the femoral component is zero degrees (perfect match)).
8. Chi1 (χ1), Hip-Knee-Ankle (HKA) angle: Alfa1 + Beta1

Part 2. Full-length standing radiographs

Timing:

Performed preoperatively and at 3 months follow-up.

Positioning:

Patient standing with toes pointing in a straight forward direction and the knees in full extension

Definitions:

Mechanical axis of femur: Centre of hip to centre of prosthetic knee
Mechanical axis of tibia: Centre of prosthetic knee to centre of ankle

Centre of preoperative (native) knee (Figure F): A point between centre of femoral notch and tibial spines is extrapolated perpendicularly down to the joint line [32].

Centre of hip: Circles are used to identify the centre of rotation of the hip (Fig.G)
Centre of the prosthetic knee: A perpendicular of the femoral condylar tangent pointing to the deepest point of the intercondylar groove. The crossing of the perpendicular line and the tangent defines the prosthetic centre (Fig.G)
Centre of the ankle: Centre of a line from medial to lateral talar body (Fig.G)

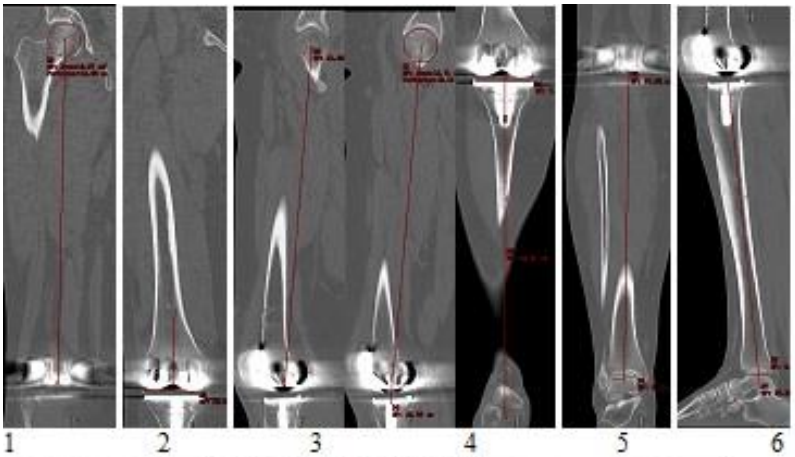
Measures:

Alignment of the prosthetic knee

1. Chi2 ($\chi 2$), Hip-Knee-Ankle (HKA) angle: Angle between mechanical axes of femur and tibia (Fig.G)
2. Alfa2 ($\alpha 2$), Alignment of the femoral component: Angle between femoral condylar joint line and mechanical axis of the femur (Fig.H1)
3. Beta2 ($\beta 2$), Alignment of the tibial component: Angle between femoral condylar joint line and mechanical axis of the tibia (Fig.H2)

Alignment of the preoperative (native) knee (Fig.G)

4. Chi0 ($\chi 0$), HKA-angle: Angle between mechanical axes of native femur and native tibia.



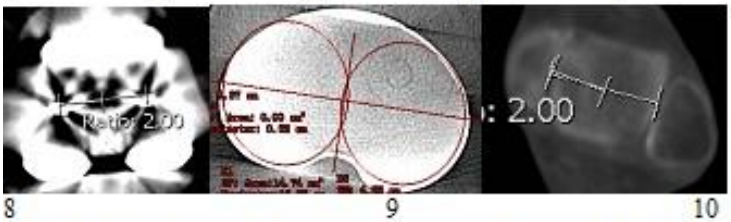


Figure A 1-10. Showing cross-bearing of coronal, sagittal and axial views to find mechanical axes of the prosthetic femur and tibia.

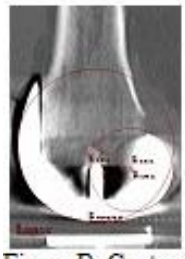


Figure B. Centre of rotation of the femoral component[6].

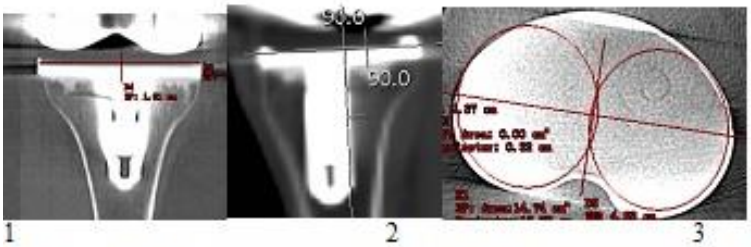
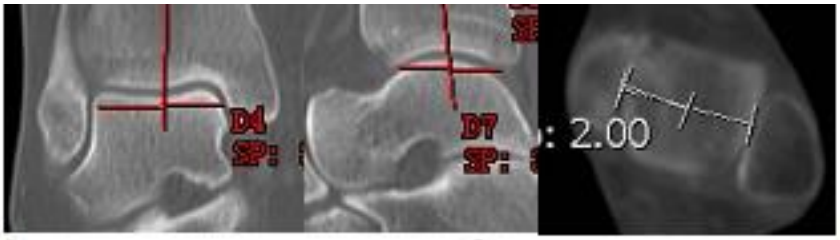


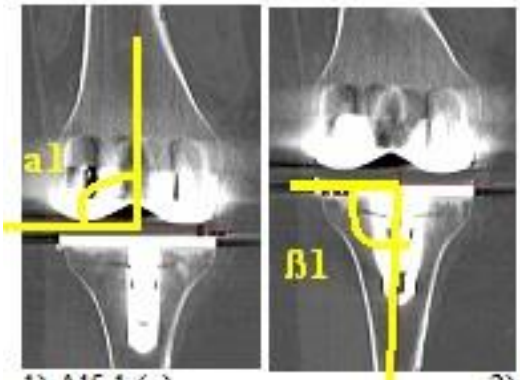
Figure C. The stem is somewhat medialized in the Profix tibia component, thus the centre of the component is somewhat lateral to the centre of the stem.

Figure A1: Appendix

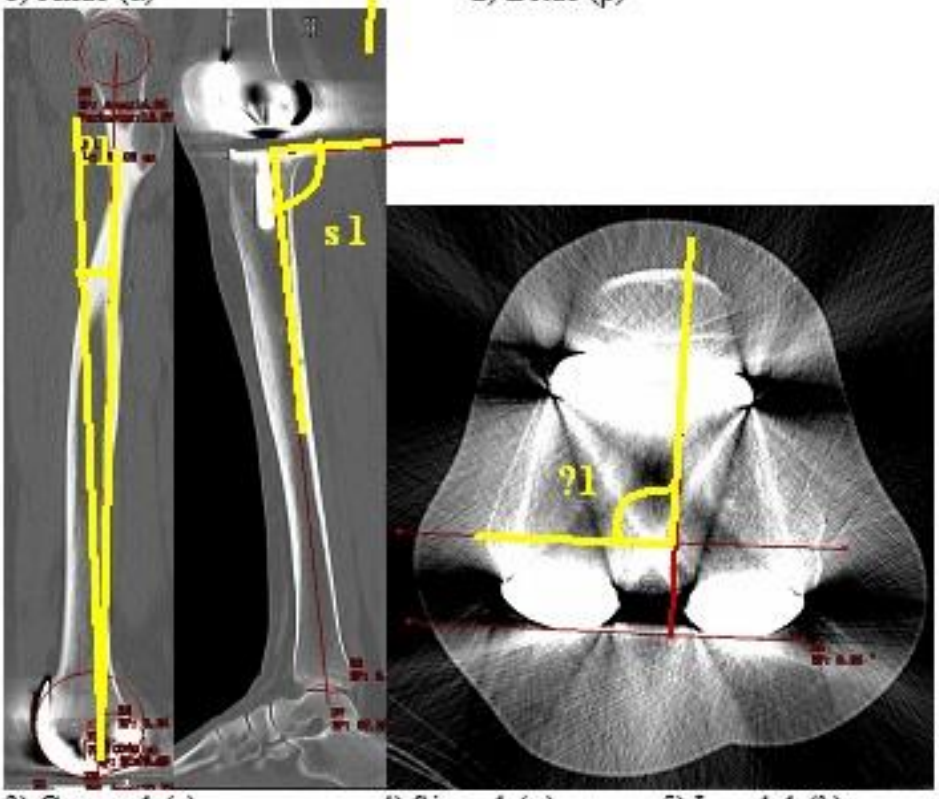


1 2 3

Figure D. Centre of the ankle in coronal (1), sagittal (2) and axial (3) views.

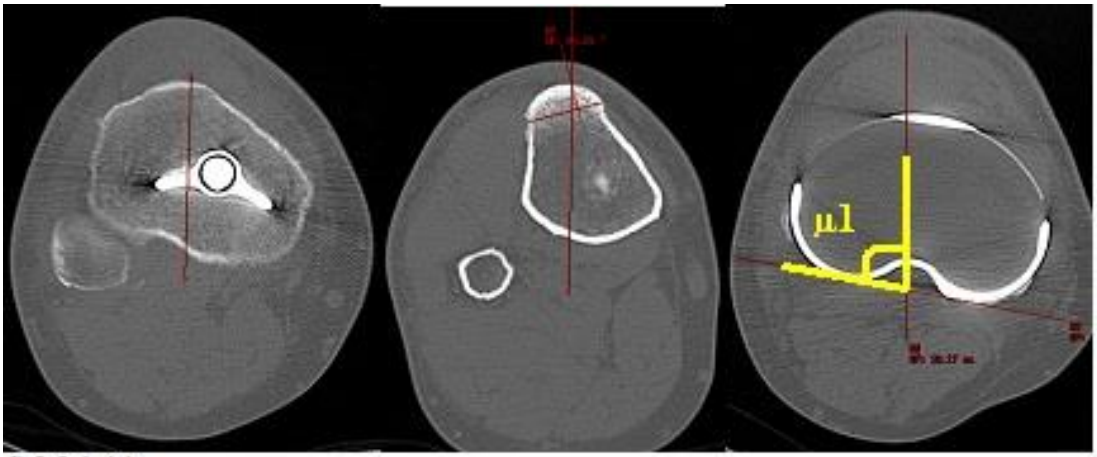


1) Alfa1 (α) 2) Beta1 (β)

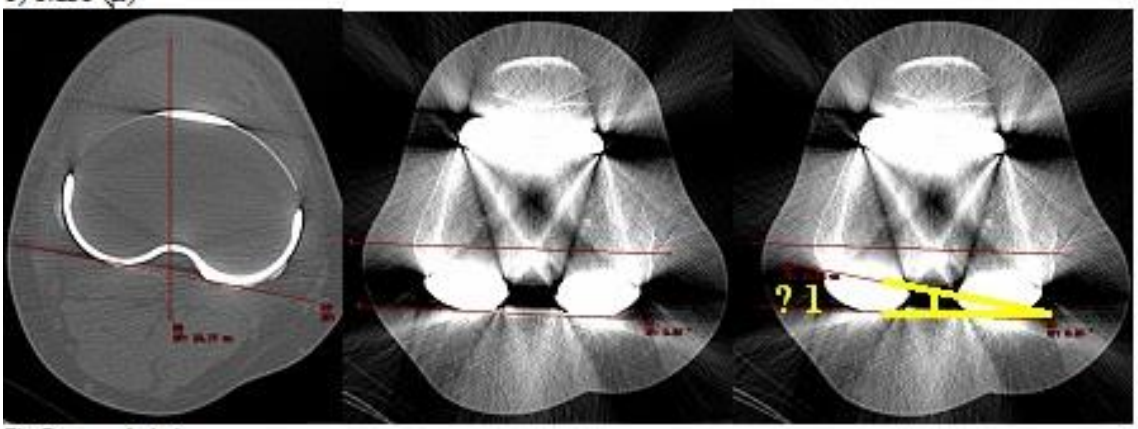


3) Gamma1 (γ) 4) Sigma1 (σ) 5) Lamda1 (λ)

Figure A2: Appendix



6) Mu1 (μ)



7) Omega1 (ω)

Figure E.1-7. Measuring the angles: alfa, beta, gamma, sigma, lambda, mu, and omega.

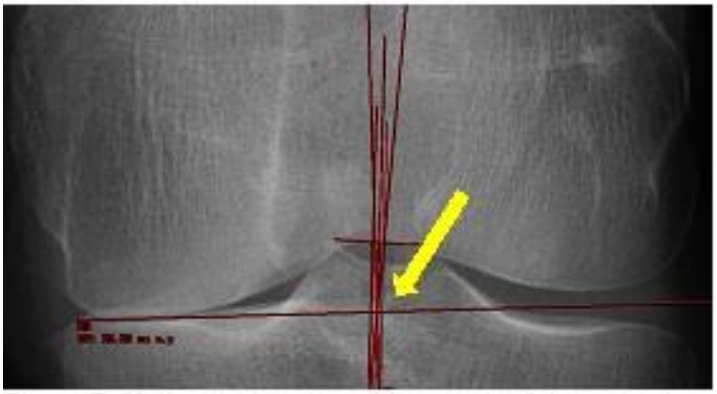


Figure F. Yellow arrow shows the centre of the native knee. A point between the centre of the femoral notch and the tibial spines is extrapolated perpendicularly down to the joint line.

Figure A3: Appendix

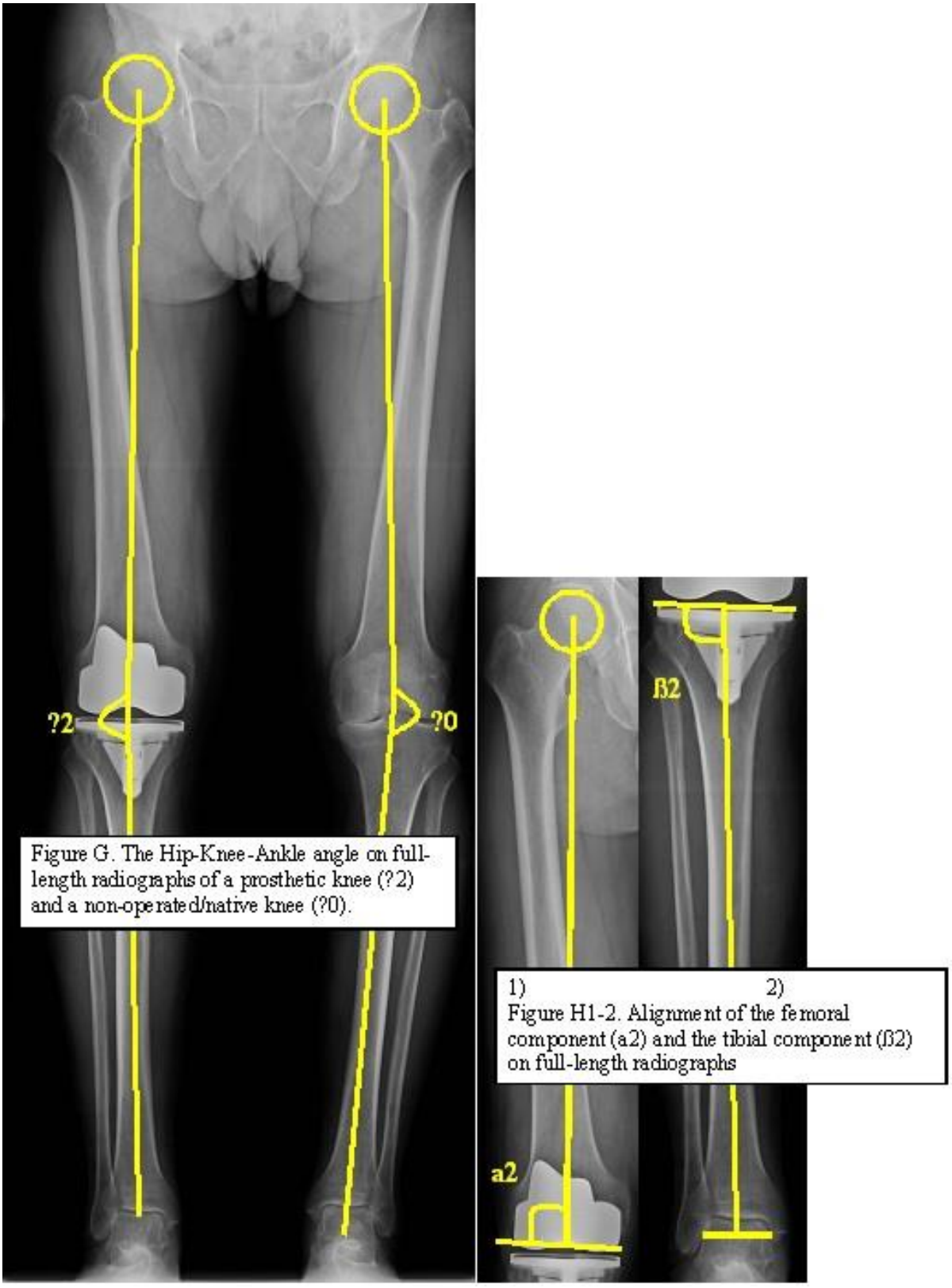


Figure A4: Appendix

10. Appendices

Appendix 1 Registration form TKR, Norwegian Arthroplasty Register

Appendix 2 Clinical Investigation Plan

Appendix 3 KSS

Appendix 4 Explanations to the KSS

Appendix 5 KSS calculations

Appendix 6 VAS

Appendix 7 EQ-5D

Appendix 8 EQ-5D User Guide 2008

Appendix 9 EQ-5D syntax

Appendix 10 KOOS

Appendix 11 KOOS & WOMAC calculations, User Guide 2003

Appendix 12 Information letter and consent, RCT

Appendix 13 CT scan and radiography protocol

Appendix 14 Randomization procedure

Appendix 15 Patient form

The Norwegian Arthroplasty Register
Department of orthopaedic surgery, Helse Bergen HF
Haukeland University Hospital
Møllendalsbakken 11, N-5021 BERGEN
Telephone +47 55973742/55973743

Personal ID (11 digits):.....

Name:.....

(Write clearly, or use patient sticker – specify hospital)

Hospital:.....

KNEE PROSTHESES and other joints

Insertion, exchange or removal of one or more prosthetic parts

LOCALISATION
- ☐1 Knee
- ☐2 Ankle
- ☐3 Toe (report joint)……..
- ☐4 Shoulder
- ☐5 Elbow
- ☐6 Wrist
- ☐7 Finger (report joint)……
- ☐8 Other……
- ☐9 Back (report level)……

HIP (one mark only) (Bilateral operations = two forms)
☐1 Right ☐2 Left

PREVIOUS OPERATION IN INDEX JOINT (more than one mark possible)
- ☐0 No
- ☐1 Osteosynthesis for intraarticular fracture
- ☐2 Osteotomy
- ☐3 Arthrodesis
- ☐4 Prosthesis
- ☐5 Synovectomy
- ☐6 Other (e.g. meniscal and ligament operations)……

DATE OF OPERATION (dd.mm.yy) |__|__| |__|__| |__|__|

INDEX OPERATION (one mark only)
☐1 Primary ☐2 Reoperation (previous prosthesis)

INDEX OPERATION (CHOOSE OPTIONS UNDER A OR B)

A . Primary operation because (more than one mark possible)	B . Reoperation because (more than one mark possible)
☐1 Idiopatisc arthrosis	☐1 Loose proximal component
☐2 Rheumatoid arthritis	☐2 Loose distal component
☐3 Sequelae, fracture……	☐3 Loose patella component
☐4 Ankylosing spondylitis	☐4 Dislocation of patella
☐5 Sequelae, ligament tear	☐5 Dislocation (not patella)
☐6 Sequelae, meniscal tear	☐6 Instability
☐7 Acute fracture	☐7 Malalignment
☐8 Sequelae,infection	☐8 Deep infection
☐9 Spondylosis	☐9 Fracture(near the prosthesis)
☐10 Sequelae, disc herniation surgery	☐10 Pain
☐11 Degenerative disc disease	☐11 Defect polyethylene
☐12 Other ……	Which part……
	☐12 Other (e.g. prev. removed prosth.)……

TYPE OF REOPERATION (more than one mark possible)
- ☐1 Exchange of distal component
- ☐2 Exchange of proximal component
- ☐3 Exchange of all components
- ☐4 Exchange of patella components
- ☐5 Exchange of polyethylene (e.g. tibia, ulna, humerus)
- ☐6 Removal of prosthestic parts Components:… ……
- ☐7 Other ……
- ☐ Insert of patella comp.

BONE TRANSPLANT (more than one mark possible)
Proximal ☐0 No ☐1 Yes ☐2 Bone impaction
Distal ☐0 No ☐1 Yes ☐2 Bone impaction

SYSTEMIC ANTIBIOTIC PROPHYLAXIS
☐0 No ☐1 Yes, type (A).....
Dose (A).....Total number of doses.....Duration ……..hrs
Possibly in combination with (B).....
Dose (B).....Total number of doses.....Duration ……..hrs

OPERATION TIME (skin-to-skin) ……minutes

PEROPERATIVE COMPLICATION
☐0 No
☐1 Yes, which .....

THROMBOSIS PROPHYLAXIS
☐0 No ☐1 Yes, which type……
Dosage day of operation……First dose given preop. ☐0 No ☐1 Yes
Later dosage……Assumed duration…….days
Possibly in combination with ……..
Dosage…….. Assumed duration……days
Stocking ☐0 No ☐1 Leg ☐2 Leg + Thigh Assumed duration…….days
Mechanical pump ☐0 No ☐1 Foot ☐2 Leg Assumed duration…….days

MINIMAL INVASIVE SURGERY (MIS) ☐0 No ☐1 Yes
COMPUTER NAVIGATION (CAOS) ☐0 No ☐1 Yes
Type of navigation ……..

ASA CLASSIFICATION (see back of the form for a definition)
- ☐1 Normal healthy
- ☐2 Mild systemic disease
- ☐3 Severe systemic disease
- ☐4 Severe systemic disease that is a constant threat to life
- ☐5 Moribund

PROSTHESIS (specify accurate, or place sticker on back of the form)

KNEE

PROSTHESIS TYPE
☐1 Tricondylar ☐3 Unicondylar ☐4 Patellofemoral
☐2 Bicondylar ☐5 Bi-compartmental ☐6 Hinged
☐ Medial ☐ Lateral

FEMORAL COMPONENT
Name/Type/Size……
Catalogue number ……
Stem ☐0 No ☐1 Yes, length ……mm
Wedge ☐0 No ☐1 Yes
Stabilized ☐0 No ☐1 Yes, posterior ☐2 Yes, other
☐1 Cement with antibiotics – Name……..
☐2 Cement without antibiotics – Name ……
☐3 Uncemented

TIBIAL COMPONENT (baseplate)
Name/Type/Size……
Catalogue number ……
Stabilized pegs ☐0 No ☐1 Yes, PE ☐2 Yes,metal ☐3 Yes,1 + 2
Extended stem ☐0 No ☐1 Yes, length…… ……mm
Wedge ☐0 No ☐1 Yes
☐1 Cement with antibiotics – Name……..
☐2 Cement without antibiotics – Name ……
☐3 Uncemented

TIBIAL COMPONENT (polyethylene insert)
Name/Type/Size……
Catalogue number ……
Thickness…….. mm
Stabilized ☐0 No ☐1 Yes, posterior ☐2 Yes, other

PATELLA COMPONENT
Name/Type/Size……
Catalogue number ……
Metal back ☐0 No ☐1 Yes
☐1 Cement with antibiotics – Name……..
☐2 Cement without antibiotics – Name ……
☐3 Uncemented

CRUCIATE LIGAMENTS

Anterior, intact before operation	☐0 No	☐1 Yes
Anterior, intact after operation	☐0 No	☐1 Yes
Posterior, intact before operation	☐0 No	☐1 Yes
Posterior, intact after operation	☐0 No	☐1 Yes

OTHER JOINTS

PROSTHESIS TYPE
☐1 Total ☐2 Hemi ☐3 One component

PROXIMAL COMPONENT
Name/Type/Size……
Catalogue number ……
☐1 Cement with antibiotics – Name……..
☐2 Cement without antibiotics – Name ……
☐3 Uncemented

DISTAL COMPONENT
Name/Type/Size……
Catalogue number ……
☐1 Cement with antibiotics – Name……..
☐2 Cement without antibiotics – Name ……
☐3 Uncemented

INTERMEDIATE COMPONENT (e.g. caput humeri)
Name/Type/Size/Diameter……
Catalogue number ……

Doctor .....
Doctor that filled in the form (name will not be registered).

Protocol

1) Introduction: We will perform a prospective, randomised, clinically controlled RSA trial comparing:

a. Profix cemented bicompartmental knee prosthesis implanted with conventional intramedullary instruments
vs
b. Profix cemented bicompartmental knee prosthesis implanted with the use of computer navigation (from Brainlab)

The trial will take place at the orthopaedic departments in four hospitals: Haukeland university hospital, Haugesund hospital, Haugesund sanitetsforening rheumatism hospital and Lovisenberg diakonale hospital.The aim is to compare the technical results (implant positioning and stability) for the Profix knee prosthesis, the perioperative morbidity and the clinical and functional results comparing the two stategies. We will also evaluate the health economical aspect through a cost-effectiveness analysis. To complete the project we will analyse data from the Norwegian arthroplasty register with respect to the two different strategies. A doctoral fellowship is part of the project.

2) Background:
In arthroplastic surgery, scientific evidence is often lacking. Haukeland university hospital in Bergen and the Norwegian arthroplasty register are closely tied, and it is natural for us to critically evaluate the usefulnes and evidence of new implants and instrumentation. Computer assisted surgery is well documented in neurosurgery, but there have been a few trials in knee replacement surgery suggesting its usefulness. Some of these trials show a better alignment and positioning of the implants (1,10,12). In addition, retrospective trials have shown that the alignment is predictive of implant survival i.e. good alignment gives a better implant survival. (7,8,9) Indirectly that may indicate computer navigation is superior in regard to implant survival. Further one might assume that a better alignment gives a better functional outcome, and this new surgical technique may be less invasive, thus leading to a faster recovery. These questions still remain unanswered.

3)Challenges:
To date there are no long term studies confirming a definite association between computer navigation and better long term results for knee replacements. No trials have thoroughly investigated the possible change in functional outcome and morbidity after the introduction of computer navigation.

4)Objectives:
We seek to find the best treatment for gonarthitic patients in need of a knee replacement.

1. In this trial we investigate whether there is a definite correlation between computer navigated knee replacements and a better long term survival of the implants. Radiostereometric analysis (RSA) will reveal micromotion of the implants and from other trials we know this can predict the long term survival of the implants (19,20).
2. Some trials have reported a higher perioperative morbidity for patients treated conventionally, as opposed to those treated with the assistance of computer navigation (1,11). Intramedullary rods may increase bleeding, and may give a higher frequency of postoperative delirium from microemboli and metabolic disturbances (16). On the

other hand, the computer navigation is often more time consuming, and can lead to a higher risk of infection. The fixation of pin-fixators in femur and tibia for the reflection beads might weaken the bone and induce a fracture risk zone. We see that both positive and negative aspects of the computer navigation technique will be revealed in this trial.

3. The computer navigation software, hardware and surgical instruments add costs to the knee replacement procedure. Hence, it is important to evaluate the benefit as compared to the costs. We will analyse this using registry data and a Markov decision analysis.
4. The Norwegian arthroplasty register has data from all Norwegian hospitals. These data will be analysed and published with regard to computer navigated knee replacement.

5) Method:

We will randomise Profix cemented bicompartmental total knee implanted conventionally vs the same prosthesis implanted with the assistance of computer navigation. Profix is the standard implant in Helse Vest and it has good 5-year implant survival data in our Norwegian arthroplasty register (15).Tantalum markers will be injected into the bone and the implant for radiostereometric analysis (RSA). The radiographic technique is somewhat challenging and we have recruited specially trained and educated radiographers to obtain these images.The images allow us to localise every marker in a three dimensional coordinate system. Mathematic models will then calculate differences in position from one image to another. Micromotion down to 0,1mm and 0,2 degrees will be detected. Micromotions within the first two years correlate with long term implant survival. The radiation dose is low (10-20% of a regular x-ray of the knee). The image processing and the calculations are time consuming and expensive. Special software is needed and we therefore collaborate with Kompetansesenter for ortopediske implantater by Norges teknisk-naturvitenskapelige universitet (NTNU).
Prior to the inclusion of patients, every surgeon has performed more than 10 knee replacements with computer assistance. All surgeons are skilled and have performed more than 100 knee replacements with the conventional technique. A pilot study with 12 patients (6 in each group) will be performed. A total of 200 patients (100 in each group) will be included in the trial.
Only 60 patients will be included in the RSA part of the trial. The precision of the RSA will be evaluated by double investigations at a 1-year follow-up. The patient receives two images separated by a short period of time. The patient is first radiographed, then he/she takes a walk in the investigation room, and is then radiographed again. Micromotion between these two images is not real, so then we know the precision of our method. The limits for significant differences are calculated as 99% confidence intervals of absolute differences for the double investigation. The upper limits for ”mean error of rigid body fitting” and ”condition number” are set to 0,35mm and 130. These parameters describe the stability of the marker and the spreading, and expresses the precision of the software. At least 20 patients are needed in each group, but the technical demanding procedure has a drop-out risk, leading us to include 30 patients in each group (23).
We aim to reveal a difference of 0,5 degrees in the two groups with alignment in the frontal plane as measured on the CT-scan. Earlier research in this field indicates a greater variation in the conventional group (standard deviation=1,3) than in the computer navigated group (standard deviation=0,9) (10). With 80% statistical power and a significance level of 0.05, a power calculation suggests 79 patients in each group. Further, to be able to detect a difference of 10 units in our functional score (KOOS)(13) with a common standard deviation of 20 (14), our power calculations suggested 94 patients in each group to reach a power of 80% at a

significance level of 0,05. From these calculations we chose a study design with 100 patients in each group, assuming there will be some drop-outs. The study is recommended by the Regional ethics committee, Personvernombudet for forskning (Norsk samfunnsvitenskapelig datatjeneste) and Statens strålevern.

6) Main activities and milestones:
Cost-effectiveness analysis 2009
Inclusion and surgery, 2009
Analysing CT scans and functional results, spring and summer 2010
Publication of 3 months follow-up winter 2010/2011
Analysing RSA results winter and spring 2012
Publication of RSA results summer and fall 2012
Register analysis, 2011

7)Scientific impact:
There are many new and expensive instrumentations and implants on the market today. In order for Norwegian hospitals to be able to offer a high international standard of treatment, we need to evaluate carefully before choices are made. To date, computer navigation in knee replacement surgery is not well documented to be recommended as a standard procedure at all Norwegian hospitals. Earlier studies are lacking in that they have not reported an impact on long term implant survival. This study is unique by using RSA to predict long term outcome. It is also large enough to evaluate functional results and morbidity. In addition, the register analysis will give us information that has not been published. It is important for the patient to be confident that he/she receives the best treatment available, and it is important for the health care providers and funding authorities to receive clear and accurate information when choosing between two different treatments, in order to gain the most benefit.

8)Dissemination of project results:
We will publish our results in high impact international medical journals to disseminate the results to colleagues around the world. Lectures and presentations in national and international congresses is a natural way to publish the results. An investigator education programme, PhD, is incorporated in the project, which includes presentations and posters in national and international congresses. The project will be registered in an international trial register, according to demands by many journals before publishing.

9) Budget:

Payroll and indirect expences for R&D personell:	**per year**	**3 years**
Doctoral research fellowship	641000,-	1923000,-
Project manager, 4 hrs/week, (0,0016*kr753500,-*192hrs)	77158,4,-	231475,-
Physiotherapist follow-up (200 patients*4 follow-ups*kr200,-)	53333,3,-	160000,-
Project secretarian 2hrs/week (,0016*220000,-*96hrs)	33792,-	101376,-
Office assistance (Innovest, 10% of sum total kr 4903400,-)	163446,6	490340,-
Total	968730,4	2906191,-

Procurement of R&D services:

Radiostereometric analysis, Trondheim (240 investigations*kr960,-)	76800,-	230400,-
Radiographer RSA, (240 investigations * kr430,-)	34400,-	103200,-

CT scan, X-ray (2000 investigations * kr900,-)	600000,-	1800000,-
Total	711200,-	2133600,-

Equipment:

Tantalum markers no.1000	5983,-	17950,-
2 injectors for tantalum markers	18000,-	54000,-
3 RSA-cages a kr 77000,-	77000,-	231000,-
Total	100983,-	302949,-

Other operating expences:

ICT, database	17000,-	51000,-
Total	17000,-	51000,-

Sum total (office assistance from Innovest included)	1797913,3	5393740,-

10) Project summary:

Background: Computer navigation in knee replacement surgery is increasingly being used around the world, but the documentation of its usefulness is lacking. In order to critically evaluate this new surgical method, we want to perform a prospective, randomised clinical trial.

Goal: We evaluate the need for these highly advanced techniques in knee replacement surgery, and the cost-effectiveness. Long term outcome for the patients will be predicted by using the radiostereometric analysis (RSA). Also, data from the Norwegian arthroplasty register will indicate any difference in long term survival of the implant. If there are any differences in the functional outcome or complication rate, between the two groups, this will be detected in this trial.

Method: Patients age 60 through 80 years old, with gonarthritis, in need of knee replacement, are included in the trial. Radiostereometric analysis (RSA), CT-scans, X-rays, clinical evaluation score systems and laboratory measures are used in the evaluation process. A cost-effective analysis is performed based on data from Norwegian life tables, data from SINTEF and from the Norwegian arthroplasty register. Data from the Norwegian arthroplasty register will be statistically analysed separately for all knee replacements done with computer navigation in Norway in the last 5 years. Four Norwegian hospitals will collaborate in this trial (Haukeland university hospital, Haugesund hospital, Haugesund sanitetsforenings hospital for rheumatic diseases and Lovisenberg diakonale hospital) and patients are recuited from all four hospitals.

Scientific impact/challenges: This trial will probably have great impact since good evidence supporting the use of computer navigation in knee surgery is lacking. It is important for the patient to be confident that he/she receives the best treatment, and it is important for the health care providers and funding authorities to have clear evidence when choosing between two different treatment techniques, in order for the patient to benefit.

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Pasientnummer:.....

American Knee Society Score (KSS)

Sett kryss ved svaret som best beskriver ditt kne

1.Hvor mye smerter har du fra kneet ditt når du går?	**2.Hvor mye smerter har du i kneet når du går opp eller ned trapper?**
☐ Ingen ☐ Lette/periodevise ☐ Moderate ☐ Svært store	☐ Ingen ☐ Lette/periodevise ☐ Moderate ☐ Svært store
3.Hvor mye smerter har du i kneet ditt når du er i ro? ☐ Ingen ☐ Lette ☐ Moderate ☐ Svært store	**4.Hvordan påvirker kneet gangfunksjonen din?** ☐ Jeg kan gå ubegrenset langt ☐ Jeg kan gå 1 – 2 km ☐ ½ til 1 km ☐ Jeg kan gå < 500 meter ☐ Jeg kan ikke gå utenfor huset ☐ Jeg kan ikke gå
5.Hvordan går du opp/ned trapper? ☐ Jeg går normalt opp og ned trapper, med en fot foran den andre ☐ Jeg går normalt opp, men må bruke rekkverket ned ☐ Jeg bruker rekkverket både opp og ned ☐ Jeg bruker rekkverket opp, kan ikke gå ned ☐ Jeg kan ikke gå i trapper	**6.Hvilken støtte bruker du når du går?** ☐ Ingen ☐ En stokk eller en krykke ☐ To stokker ☐ To krykker ☐ Rullator

<u>Klinisk vurdering av kneet</u>

7. **Grader bevegelse** (fra maksimal aktiv strekk til maksimal aktiv bøy) _____Grader
8. **Mangler på full aktiv strekk (extension lag)** _____Grader
9. **Mangler på passiv strekk (flexion contracture)** _____Grader

10.Medial/lateral stabilitet (20 grader fleksjon)	**11.Anterior/Posterior stabilitet (skuffetest)**
☐ 0-5 mm ☐ 5-10 mm ☐ >10 mm	☐ 0-5 mm ☐ 5-10 mm ☐ >10 mm

12.Akseavvik (Varus eller valgusfeilstilling i forhold til 0 grader mekanisk akse, klinisk bedømt)_____Grader

Kommentar og veiledning til kneundersøkelsen i KSS

Punkt 7:
Mål med goniometer fra mest laterale punkt/midt på trochanter, omdreiningspunkt på laterale epicondyl, og distale punkt på mest laterale punkt/midt på laterale malleol.

Punkt 8:
Mål med goniometer (som over) hvor mye som mangler på full strekk ved **akti**v ekstensjon.

Punkt 9:
Mål med goniometer (som over) hvor mye som mangler på full strekk ved **passivt** strekk.

Punkt 10/11:
Tas på øyemål, men gjerne med en finger i leddspalten. Det er slik vi måler grad 1, grad 2 og grad 3 instabilitet som tilsvarer de tre utfallene i KSS.

Punkt 12:
Mål på strakt kne (evt mest mulig strakt) på følgende måte:

1. Finn spina iliaca ant sup og gå to fingerbredder medialt.
2. Finn punktet midt mellom malleolene.
3. Legg goniometer midt på kneet med omdreiningspunktet i leddspaltenivå like i underkant (distalt) av patellaspissen.
4. Les av vinkelen.

Utregning av poeng i punkt 1. 2. og 3. i KSS

Ingen smerter: 1.1 + 2.1 + 3.1 = 50 p
Letter periodevise smerter:
1.2 = 45 p
3.2 = 45 p
1.2 + 3.2 = 45 p
Lette periodevise smerter, bare i trapper: 2.2 = 40 p
Lette periodevise smerter, trapper og gange: 1.2 + 2.2 = 30 p
Moderate smerter, periodevis:
1.3 = 20 p
2.3 = 20 p
1.3 + 2.3 = 20 p
Moderate smerter, kontinuerlig: 3.3 = 10 p
Svært store smerter:
1.4 = 0 p
2.4 = 0 p
3.4 = 0 p

Til punkt 6: 6.4 og 6.5: Begge punkt gir fratrekk på 20 poeng.
6.3 gir bare 10 poeng fratrekk.

Til punkt 10: 1mm tilsvarer 1 grad. Mediolateral instabilitet > 15 mm/grader mangler av en eller annen grunn i denne versjonen. Vi må sette > 10 mm/grader = 5 p også på de med instabilitet > 15 grader, siden vi nå har over 30 pasienter som ikke har med denne siste kategorien.

Missing data: (behandles som i KOOS, siden vi ikke har noen nærmere beskrivelse når det gjelder KSS)
Hvis bommet på boksen, brukes den boksen som er nærmest. Hvis to bokser er krysset av brukes den mest alvorlige kategorien. Hvis det mangler data innenfor en kategori, scores gjennomsnittsverdien (halvparten av max-verdi) for den aktuelle kategorien, feks er maks poeng 50 i kategori 1 (spsm 1), og gjennomsnittsverdi angis som 25 p.

VAS – Visual analogue scale

Merk av på linjen nedenfor hvordan du opplever smertene i kneet

Høyre kne:

Ingen smerte _____Uutholdelige smerter

Venstre kne:

Ingen smerte _____Uutholdelige smerter

EQ-5D

I de 5 neste spørsmålene ønsker vi å vite hvordan livssituasjonen din er NÅ.
Sett ring rundt det svaret som passer best:

1. Hvordan opplever du gangevnen din?

1 Jeg har ingen problemer med å gå omkring
2 Jeg har litt problemer med å gå omkring
3 Jeg er sengeliggende

2. Hvordan klarer du personlig stell?

1 Jeg har ingen problemer med personlig stell
2 Jeg har litt problemer med å vaske meg eller kle meg
3 Jeg klarer ikke å vaske meg eller kle meg

3. Hvordan klarer du dine vanlige gjøremål (f.eks. arbeid, studier, husarbeid, familie- og fritidsaktiviteter)?

1 Jeg har ingen problemer med å utføre mine vanlige gjøremål
2 Jeg har litt problemer med å utføre mine vanlige gjøremål
3 Jeg er ute av stand til å utføre mine vanlige gjøremål

4. Smerter eller ubehag?

1 Jeg har verken smerte eller ubehag
2 Jeg har moderat smerte eller ubehag
3 Jeg har sterk smerte eller ubehag

5. Angst eller depresjon?

1 Jeg er verken engstelig eller deprimert
2 Jeg er noe engstelig eller deprimert
3 Jeg er svært engstelig eller deprimert

User Guide

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Version 1.0

August 2008

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Table of contents

1. Introduction

This guide has been developed in order to give users of EQ-5D basic information on how to use EQ-5D. Topics include administering the instrument, setting up a database for data collected using EQ-5D as well as information about how to present the results. Also included are some frequently asked questions dealing with common issues regarding the use of EQ-5D and a list of currently available EuroQoL products.

EuroQoL Group

- The EuroQoL Group is a network of international multidisciplinary researchers devoted to the measurement of health status. Established in 1987, the EuroQoL Group originally consisted of researchers from Europe, but nowadays includes members from North America, Asia, Africa, Australia, and New Zealand. The Group is responsible for the development of EQ-5D, a preference based measure of health status that is now widely used in clinical trials, observational studies and other health surveys.

- The EuroQoL Group has been holding annual scientific meetings since its inception in 1987.

- The EuroQoL Group can be justifiably proud of its collective scientific achievements over the last 20 years. Research areas include: valuation, EQ-5D use in clinical studies and in population surveys, experimentation with the EQ-5D descriptive system, computerized applications, interpretation of EQ-5D ratings and the role of EQ-5D in measuring social inequalities in self-reported health.

- The EuroQoL Group's website (www.euroqol.org) contains detailed information about EQ-5D, guidance for users, a list of available language versions, EQ-5D references and contact details.

EQ-5D

EQ-5D is a standardised measure of health status developed by the EuroQoL Group in order to provide a simple, generic measure of health for clinical and economic appraisal[1]. Applicable to a wide range of health conditions and treatments, it provides a simple descriptive profile and a single index value for health status that can be used in the clinical and economic evaluation of health care as well as in population health surveys (Figure 1).

EQ-5D is designed for self-completion by respondents and is ideally suited for use in postal surveys, in clinics, and in face-to-face interviews. It is cognitively undemanding, taking only a few minutes to complete. Instructions to respondents are included in the questionnaire.

EQ-5D essentially consists of 2 pages - the EQ-5D descriptive system (page 2) and the EQ visual analogue scale (EQ VAS) (page 3). The EQ-5D descriptive system comprises the following 5 dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Each dimension has 3 levels: no problems, some problems, severe problems. The respondent is asked to indicate his/her health state by ticking (or placing a cross) in the box against the most appropriate statement in each of the 5 dimensions. This decision results in a 1-digit number expressing the level selected for that dimension. The digits for 5 dimensions can be combined in a 5-digit number describing the respondent's health state. **It should be noted that the numerals 1-3 have no arithmetic properties and should not be used as a cardinal score.** This current 3-level, 5-dimensional format of EQ-5D will remain unchanged for the immediate future. However a EuroQoL task force is developing a 5-level version. This should become available around 2009.

The EQ VAS records the respondent's self-rated health on a vertical, visual analogue scale where the endpoints are labelled 'Best imaginable health state' and 'Worst imaginable health state'. This information can be used as a quantitative measure of health outcome as judged by the individual respondents.

[1] EuroQoL Group. EuroQoL-a new facility for the measurement of health-related quality of life. Health Policy 1990;16:199-208

Figure 1: EQ-5D (UK English version)

By placing a tick in one box in each group below, please indicate which statements best describe your own health state today.

Mobility

I have no problems in walking about	❑
I have some problems in walking about	❑
I am confined to bed	❑

Self-Care

I have no problems with self-care	❑
I have some problems washing or dressing myself	❑
I am unable to wash or dress myself	❑

Usual Activities (*e.g. work, study, housework, family or leisure activities)*

I have no problems with performing my usual activities	❑
I have some problems with performing my usual activities	❑
I am unable to perform my usual activities	❑

Pain/Discomfort

I have no pain or discomfort	❑
I have moderate pain or discomfort	❑
I have extreme pain or discomfort	❑

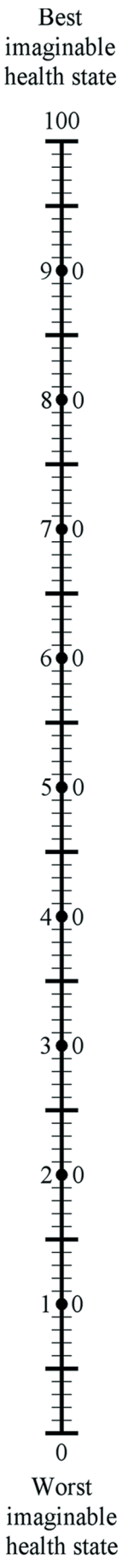
Anxiety/Depression

I am not anxious or depressed	❑
I am moderately anxious or depressed	❑
I am extremely anxious or depressed	❑

To help people say how good or bad a health state is, we have drawn a scale (rather like a thermometer) on which the best state you can imagine is marked 100 and the worst state you can imagine is marked 0.

We would like you to indicate on this scale how good or bad your own health is today, in your opinion. Please do this by drawing a line from the box below to whichever point on the scale indicates how good or bad your health state is today.

Your own health state today



What is a health state?

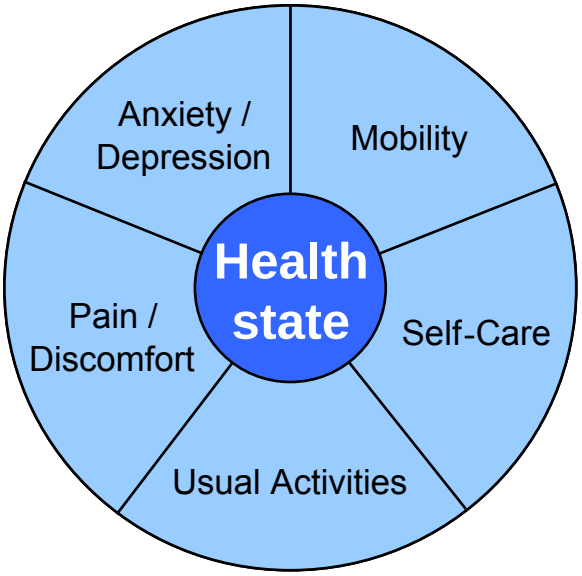
Each of the 5 dimensions comprising the EQ-5D descriptive system is divided into 3 levels of perceived problems:

Level 1: indicating no problem

Level 2: indicating some problems

Level 3: indicating extreme problems

A unique health state is defined by combining 1 level from each of the 5 dimensions.



A total of 243 possible health states is defined in this way. Each state is referred to in terms of a 5 digit code. For example, state 11111 indicates no problems on any of the 5 dimensions, while state 11223 indicates no problems with mobility and self care, some problems with performing usual activities, moderate pain or discomfort and extreme anxiety or depression.

Note: Two further states (unconscious and death) are included in the full set of 245 EQ-5D health states, but information on these states is not collected via self-report.

Versions of EQ-5D

EQ-5D in different languages

Currently there are more than 100 translated versions of EQ-5D. If you want to know if there is an EQ-5D version appropriate for your country, please consult the website.

All translations/adaptations of EQ-5D are produced using a standardised translation protocol that conforms to internationally recognized guidelines. These guidelines aim to ensure semantic and conceptual equivalence and involve a forward/backward translation process and lay panel assessment. Only the EuroQoL Group Executive Office can give permission for a translation to be performed and translations can only be stamped as official if they are performed in cooperation with EuroQoL Group reviewers.

Alternative modes of administration

EQ-5D was primarily designed for self-completion by the patient or respondent. However the Group has brief guidelines for the following alternative modes of administration:

(i) Face-to-face
(ii) Self-completion in the presence of an interviewer
(iii) Telephone interview
(iv) Proxy (asking the proxy to rate how he or she, (i.e. the proxy), would rate the subject's health)

Guidelines for telephone and proxy use are available in a number of different languages.

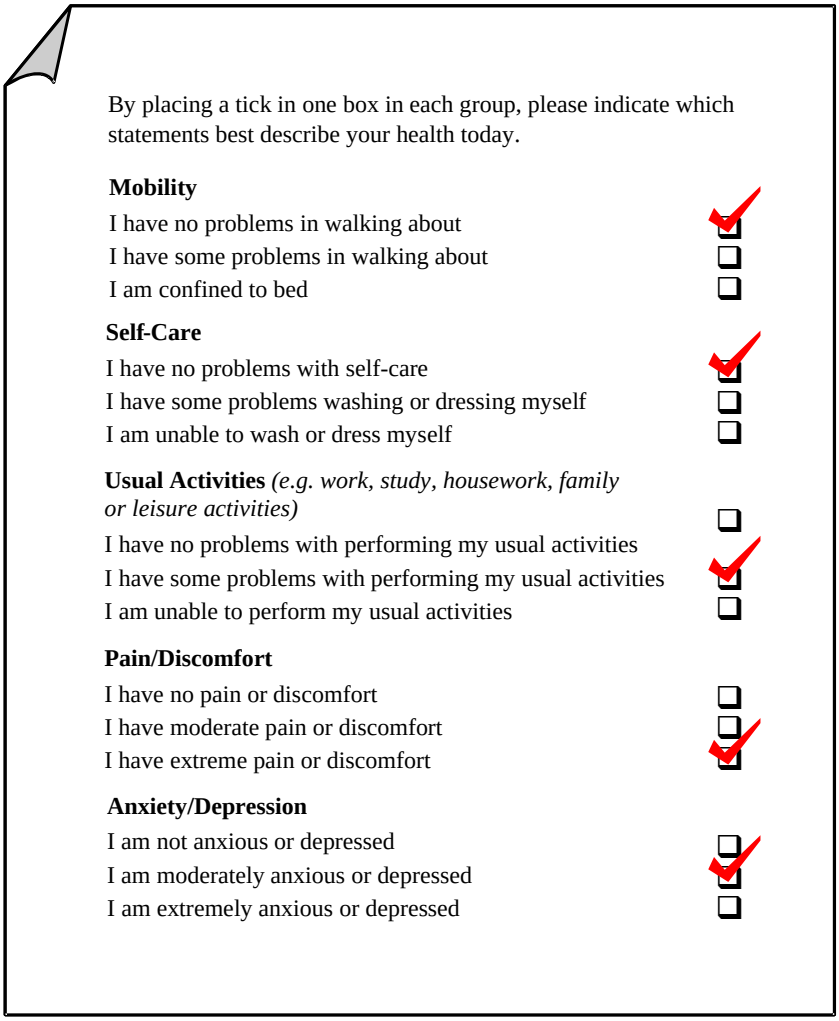
Child versions

EQ-5D is generally considered suitable for children aged 12 years and over (although this may vary in different countries). Currently a EuroQoL Group task force is developing a version for children between 7 and 12 years in international English. This version is being validated in Swedish, Italian, Spanish and German and these versions should become available in 2008.

Please check the EuroQoL website for up-to-date information on the availability of EuroQoL products.

2. Scoring the EQ-5D descriptive system

The EQ-5D descriptive system should be scored as follows:



By placing a tick in one box in each group, please indicate which statements best describe your health today.

Mobility
- ☐ I have no problems in walking about
- ☐ I have some problems in walking about
- ☑ I am confined to bed

Self-Care
- ☐ I have no problems with self-care
- ☐ I have some problems washing or dressing myself
- ☑ I am unable to wash or dress myself

Usual Activities *(e.g. work, study, housework, family or leisure activities)*
- ☐ I have no problems with performing my usual activities
- ☑ I have some problems with performing my usual activities
- ☐ I am unable to perform my usual activities

Pain/Discomfort
- ☐ I have no pain or discomfort
- ☑ I have moderate pain or discomfort
- ☐ I have extreme pain or discomfort

Anxiety/Depression
- ☐ I am not anxious or depressed
- ☑ I am moderately anxious or depressed
- ☐ I am extremely anxious or depressed

Levels of perceived problems are coded as follows:

☑ ☐ ☐	Level 1 is coded as a '1'
☐ ☑ ☐	Level 2 is coded as a '2'
☐ ☐ ☑	Level 3 is coded as a '3'

NB: There should be only <u>one</u> response for each dimension.

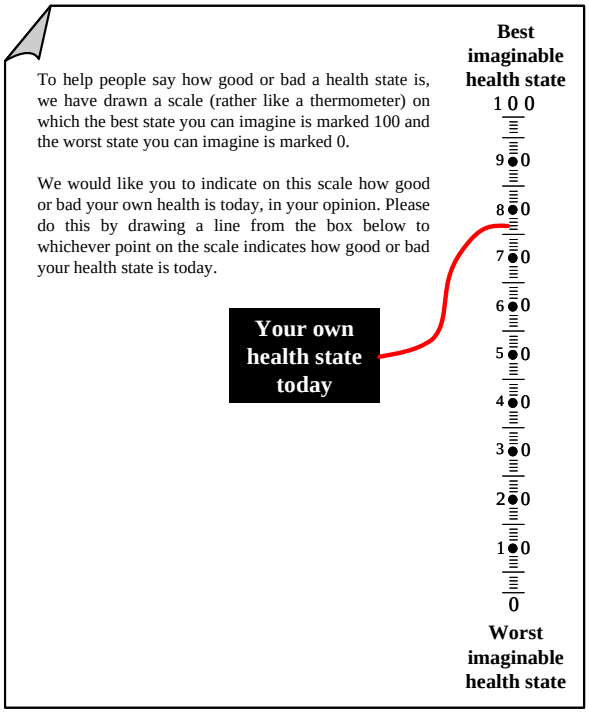
This example identifies the state 11232.

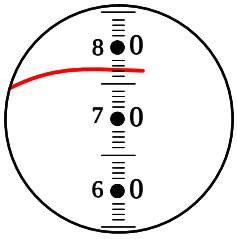
Missing values can be coded as '9'.

Ambiguous values (e.g. 2 boxes are ticked for a single dimension) should be treated as missing values.

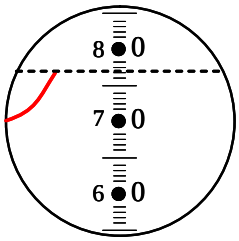
3. Scoring the EQ VAS

The EQ VAS should be scored as follows:





For example this response should be coded as 77



Even though the line does not cross the VAS this response can still be scored by drawing a horizontal line from the end point of the response to the VAS. In this example the response should be coded as 77

Missing values should be coded as '999'.

Ambiguous values (e.g. the line crosses the VAS twice) should be treated as missing values.

4. Converting EQ-5D states to a single summary index

EQ-5D health states, defined by the EQ-5D descriptive system, may be converted into a single summary index by applying a formula that essentially attaches values (also called weights) to each of the levels in each dimension. The index can be calculated by deducting the appropriate weights from 1, the value for full health (i.e. state 11111). Information in this format is useful, for example, in cost utility analysis.

Value sets have been derived for EQ-5D in several countries using the EQ-5D visual analogue scale (EQ-5D VAS) valuation technique or the time trade-off (TTO) valuation technique. The list of currently available value sets with the number of respondents and valuation technique applied is presented in table 1. Most of the EQ-5D value sets have been obtained using a representative sample of the general population, thereby ensuring that they represent the societal perspective. For anyone working with EQ-5D data, an essential guide to the Group's available value sets can be found in: EuroQoL Group Monograph series: Volume 2: EQ-5D value sets: inventory, comparative review and user guide, recently published by Springer (see section 8 for more information).

Table 1: List of available value sets as of May 2007

Country	N	Valuation method
Belgium	548	EQ-5D VAS
Denmark	1179	EQ-5D VAS
Denmark	1332	TTO
Europe	6870	EQ-5D VAS
Finland	928	EQ-5D VAS
Germany	339	EQ-5D VAS
Germany	339	TTO
Japan	543	TTO
New Zealand	919	EQ-5D VAS
Netherlands	298	TTO
Slovenia	370	EQ-5D VAS
Spain	294	EQ-5D VAS
Spain	975	TTO
UK	3395	EQ-5D VAS
UK	3395	TTO
US	3773	TTO
Zimbabwe	2384	TTO

Documents containing the scoring algorithms, information on the valuation studies, tables of values for all 243 health states and SPSS and SAS syntax files can be ordered from the EuroQoL Executive Office (userinformationservice@euroqol.org).

5. Organising EQ-5D data

Data collected using EQ-5D can be entered in a database according to the following schema:

Variable name	ID	COUNTRY	YEAR	MOBILITY	SELFCARE	ACTIVITY	PAIN	ANXIETY
Variable description	patient ID number			1=No Problems, 2=Some problems, 3=Extreme problems, 9=Missing value	1=No Problems, 2=Some problems, 3=Extreme problems, 9=Missing value	1=No Problems, 2=Some problems, 3=Extreme problems, 9=Missing value	1=No Problems, 2=Some problems, 3=Extreme problems, 9=Missing value	1=No Problems, 2=Some problems, 3=Extreme problems, 9=Missing value
Data row 1	1001	UK	2006	2	1	2	2	1
Data row 2	1002	UK	2006	1	1	1	1	1

Variable name	STATE	EQ_VAS	SEX	AGE	EDU	METHOD	SOC_ECON
Variable description		999= Missing value	1=male, 2=female, 9=Missing value	999= Missing value	1=low, 2=medium, 3=high, 9=Missing value	0=postal, 1=interview, 2=telephone, 9=Missing value	1=employed, 2=retired, ….., 9=Missing value
Data row 1	21221	80	1	43	1	0	1
Data row 2	21111	90	2	24	2	0	4

NB: The variable names are just examples. However, the variables for the 5 dimensions of the EQ-5D descriptive system should be named 'mobility', 'selfcare', 'activity', 'pain', and 'anxiety'. If they are given different names the syntax codes containing the value sets that are distributed by the EuroQoL Group will not work properly.

6. Presenting EQ-5D results

Data collected using EQ-5D can be presented in various ways. A basic subdivision can be made according to the structure of the EQ-5D:

1. Presenting results from the descriptive system as a health profile
2. Presenting results of the EQ VAS as a measure of overall self-rated health status
3. Presenting results from the descriptive system as a weighted index

However, the way results are presented is partly determined by what message you, as a researcher, wish to convey to your audience.

Health profiles

One way of presenting data as a health profile is by making a table with the frequency or the proportion of reported problems for each level for each dimension. These tables can be broken down to include the proportions per subgroup, such as age, before vs. after treatment, treatment vs. comparator, etc.

Sometimes it is more convenient to dichotomise the EQ-5D levels into 'no problems' (i.e. level 1) and 'problems' (i.e. levels 2 and 3), thereby changing the profile into frequencies of reported problems. This can be the case, for example, in a general population survey where the numbers of reported level 3 problems are very low. Tables 2 and 3 are examples of how to present EQ-5D data in tabulated form. The data for the tables originates from a general population survey in the UK[2].

[2]Kind P, Dolan P, Gudex C, Williams A. Variations in population health status: results from a United Kingdom national questionnaire survey Bmj 1998;316 (7133): 736-41.

Table 2: Proportion of levels 1, 2 and 3 by dimension and by age group

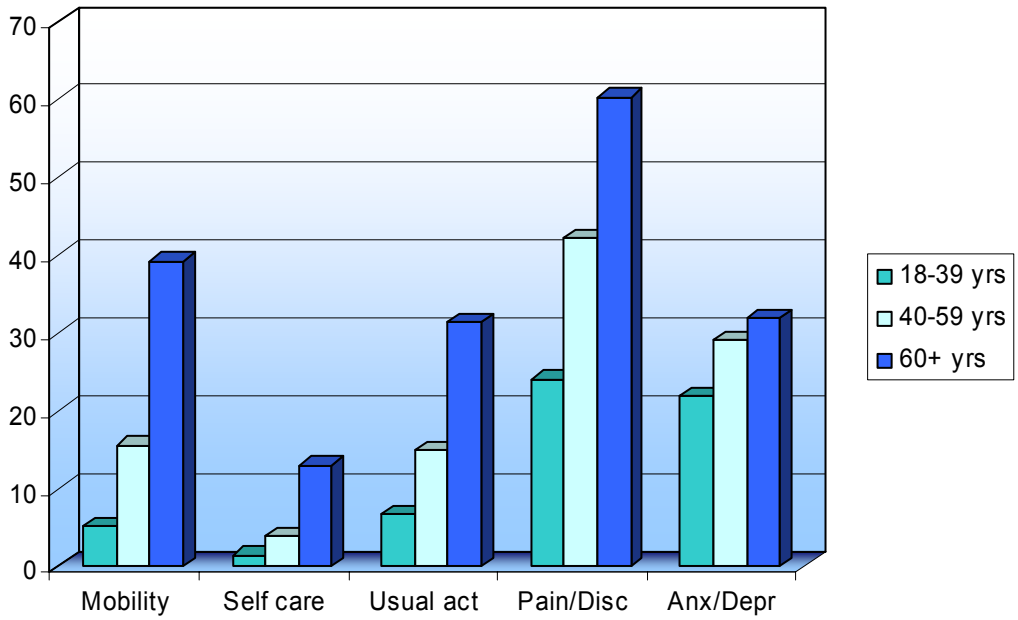
EQ-5D DIMENSION		AGE GROUPS 18-29	30-39	40-49	50-59	60-69	70-79	80+	TOTAL
MOBILITY	Level 1	95.4	92.2	89.7	78.1	70.7	60.2	43.3	81.6
	Level 2	4.6	7.6	9.9	21.9	29.3	39.8	56.7	18.3
	Level 3	0.0	0.1	0.4	0.0	0.0	0.0	0.0	0.1
SELF-CARE	Level 1	99.1	98.4	95.8	94.8	94.3	92.6	83.7	95.7
	Level 2	0.9	1.5	4.0	5.2	5.5	7.1	15.6	4.1
	Level 3	0.0	0.1	0.2	0.0	0.2	0.2	0.7	0.1
USUAL ACTIVITIES	Level 1	93.3	91.4	89.2	78.1	75.3	73.7	56.0	83.7
	Level 2	6.3	7.9	9.4	18.8	21.6	22.1	38.3	14.2
	Level 3	0.4	0.7	1.5	3.0	3.1	4.2	5.7	2.1
PAIN / DISCOMFORT	Level 1	83.9	80.7	74.1	56.3	53.8	44.0	39.7	67.0
	Level 2	15.8	17.7	22.8	38.1	40.6	48.4	49.6	29.2
	Level 3	0.3	1.6	3.1	5.6	5.6	7.6	10.6	3.8
ANXIETY / DEPRESSION	Level 1	86.5	82.6	81.3	72.8	72.0	74.7	75.2	79.1
	Level 2	12.6	16.4	16.9	24.4	25.1	22.6	24.1	19.1
	Level 3	0.9	1.0	1.8	2.8	2.9	2.7	0.7	1.8

Table 3: Frequency of reported problems by dimension and age group

EQ-5D DIMENSION		AGE GROUPS 18-29	30-39	40-49	50-59	60-69	70-79	80+	TOTAL
MOBILITY	No problems	643	631	489	362	339	246	61	2770
	Problems	31	53	56	101	140	162	81	625
SELF-CARE	No problems	668	673	522	439	452	378	119	3251
	Problems	6	11	23	24	27	30	23	144
USUAL ACTIVITIES	No problems	629	625	486	362	361	301	80	2842
	Problems	45	59	59	101	118	107	62	553
PAIN / DISCOMFORT	No problems	566	552	404	261	258	179	56	2275
	Problems	108	132	141	202	221	229	86	1120
ANXIETY / DEPRESSION	No problems	583	565	443	337	345	305	107	2684
	Problems	91	119	102	126	134	103	35	711

In addition to presenting the results in tabulated form, you can also use graphical presentations. Two or 3 dimensional bar charts can be used to summarise the results in 1 graph, (see figure 2). Figure 2 shows the sum of the proportion of reported level 2 and level 3 problems for each of the 5 EQ-5D dimensions for 3 distinct age groups. Older people reported more problems on all dimensions but the effect of age was strongest for mobility and weakest for anxiety/depression.

Figure 2: Profile of the population (% reporting problem)



EQ VAS

In order to present all aspects of the EQ VAS data, you should present both a measure of the central tendency and a measure of dispersion. This could be the mean values and the standard deviation or, if the data is skewed, the median values and the 25th and 75th percentiles. An example is presented in table 4. The data for the table originates from a general population survey in the UK[3].

Table 4: EQ VAS values by age – mean + standard deviation and median + percentiles

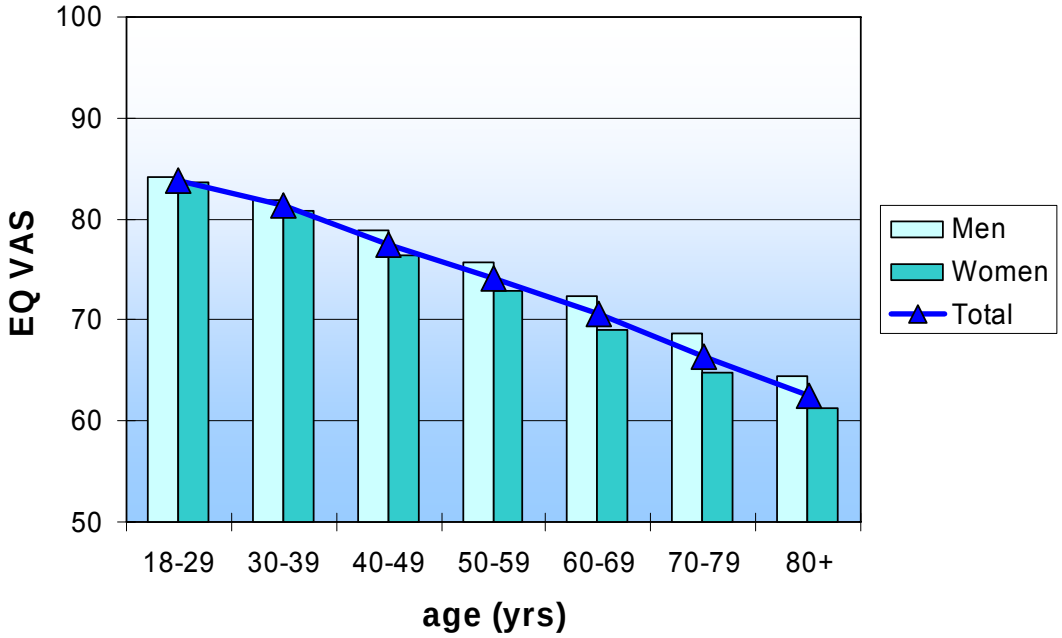
	AGE GROUPS							
EQ VAS	*18-29*	*30-39*	*40-49*	*50-59*	*60-69*	*70-79*	*80+*	*TOTAL*
Mean	87.0	86.2	85.1	81.3	79.8	75.3	72.5	82.8
- Std dev	13.8	14.6	15.5	46.8	17.5	18.5	18.2	23.1
Median	90	90	90	86	85	80	75	90
- 25th	80	80	80	70	70	65	60	75
- 75th	98	95	95	95	93	90	88	95

You can present a graphical representation of the data by using bar charts, line charts, or both (see figure 3). Figure 3 shows the mean EQ VAS ratings reported by

[3] Kind P, Dolan P, Gudex C, Williams A. Variations in population health status: results from a United Kingdom national questionnaire survey Bmj 1998;316 (7133): 736-41.

men, women and both for 7 distinct age groups. The mean EQ VAS ratings are seen to decrease with increasing age. Also, men of all age groups reported higher EQ VAS ratings than women.

Figure 3: Mean population EQ VAS ratings by age group and sex



EQ-5D index

Information about the EQ-5D index can be presented in much the same way as the EQ VAS data. This means that for the index, you can present both a measure of the central tendency and a measure of dispersion. This could be the mean values and the standard deviation (or standard error). If the data is skewed, the median values and the 25th and 75th percentiles could be presented. Tables 5 and 6 and figures 4 and 5 contain 2 examples of how to present EQ-5D index results. Table 5 and figure 4 present the results from a study where the effect of a treatment on health status is investigated. Table 6 and figure 5 show results for a patient population and 3 subgroups (the tables and figures are based on hypothetical data and for illustration purposes only).

Table 5: EQ-5D index values before and after treatment – mean + standard deviation and median + percentiles

EQ-5D index	before treatment	after treatment
Mean	0.59	0.76
- Std error	0.012	0.015
Median	0.60	0.70
- 25th	0.50	0.65
- 75th	0.70	0.80
N	120	110

Figure 4: EQ-5D index values before and after treatment – mean values and 95% confidence intervals

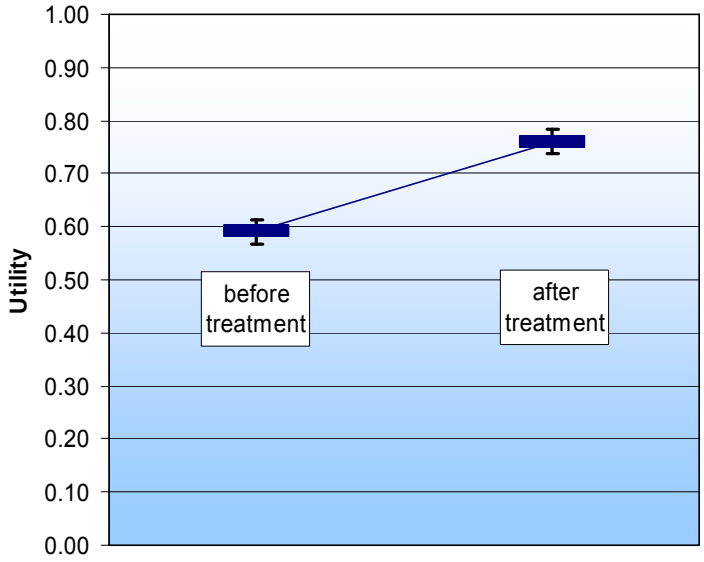
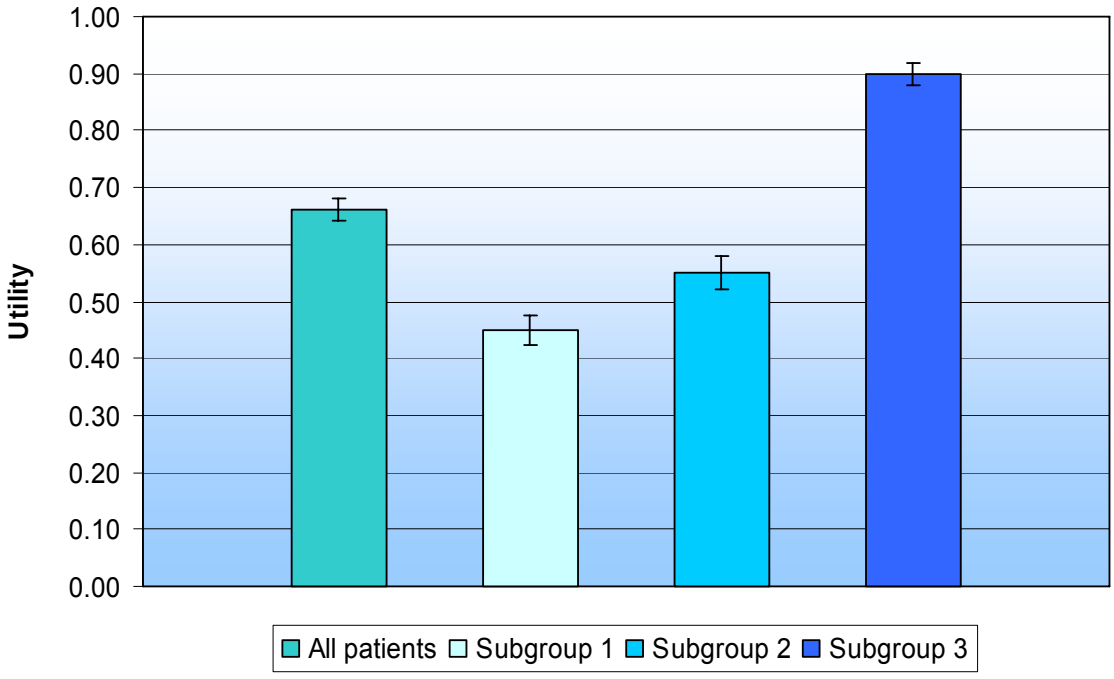


Table 6: EQ-5D index values of the total patient population and the 3 subgroups – mean + standard deviation and median + percentiles

EQ-5D-index	All patients	Subgroup 1	Subgroup 2	Subgroup 3
Mean	0.66	0.45	0.55	0.90
- Std error	0.010	0.013	0.015	0.010
Median	0.55	0.40	0.55	0.95
- 25th	0.50	0.30	0.50	0.80
- 75th	0.70	0.50	0.60	1.00
N	300	100	75	125

Figure 5: EQ-5D index values of the total patient population and the 3 subgroups – mean values and 95% confidence intervals



7. EQ-5D: Frequently asked questions

For what period of time does EQ-5D record health status?

Self-reported health status captured by EQ-5D relates to the respondent's situation at the time of completion. No attempt is made to summarise the recalled health status over the preceding days or weeks, although EQ-5D has been tested in recall mode. An early decision taken by the EuroQoL Group determined that health status measurement ought to apply to the respondent's immediate situation - hence the focus on 'your own health state today'.

General population value sets vs patient population value sets

If you want to undertake a utility analysis you will need to use a value set. Generally speaking utility analysis requires a general population-based value set (as opposed to a patient-based set). The rationale behind this is that the values are supposed to reflect the preferences of local taxpayers and potential receivers of healthcare. Additionally, patients tend to rate their health states higher than the general population because of coping etc, often underestimating their need for healthcare. The EQ-5D value sets are therefore based on the values of the general population.

Difference between the EQ-5D descriptive system and the EQ VAS

The descriptive system can be represented as a health state, e.g. health state 11212 represents a patient who indicates some problems on the usual activities and anxiety/depression dimensions. These health states can be converted to a single index value using (one of) the available EQ-5D value sets. These value sets have been derived using VAS or TTO valuation techniques, and reflect the opinion of the general population. The EQ VAS scores are patient-based and are therefore not representative of the general population. The EQ VAS self-rating records the respondent's own assessment of their health status. The EQ VAS scores however are anchored on 100 = best imaginable health and 0 = worst imaginable health, whereas the value sets are anchored on 11111 = 1 and dead = 0 and can therefore be used in QALY calculations.

Difference between the VAS and TTO techniques

The difference between the value sets based on TTO and those based on VAS is that the techniques used for the elicitation of the values on which the models are based differ. In the TTO task, respondents are asked, for example, to imagine they live in a health state (e.g. 22222) for 10 years and then asked to specify the amount of time they are willing to give up to live in full health instead (i.e. 11111). For example, someone might find 8 years in 11111 equivalent to 10 years in 22222. The VAS technique on the other hand, asks people to indicate where, on a vertical thermometer-like scale ranging from best imaginable health to worst imaginable health, they think a health state should be positioned.

Multinational clinical trials

Information relating to EQ-5D health states gathered in the context of multinational trials may be converted into a single summary index using one of the available EQ-5D value sets. There are different options available to do this using appropriate value sets-however the choice depends on the context in which the information will be used by researchers or decision makers. In cases where data from an international trial are to be used to inform decision makers in a specific country, it seems reasonable to expect decision makers to be interested primarily in value sets that reflect the values for EQ-5D health states in that specific country. So for example, if applications for reimbursement of a drug are rolled out from country to country, country-specific value sets should be applied and reported in each pharmaco-economic report. This is no different from the requirement to use country-specific costs. In the absence of a country-specific value set, the researcher should select another set of values for a population that most closely approximates that country. Sometimes however, information about utilities is required to inform researchers or decision makers in an international context. In these instances, 1 value set applied over all EQ-5D health states data is probably more appropriate.

The decision about which value set to use will also depend on whether the relevant decision making body in each country specifies any requirements or preferences in regard to the methodology used in different contexts (e.g. TTO, standard gamble (SG), VAS or discrete choice modelling (DCM)). These guidelines are the topic of an international ongoing debate but the EuroQoL website is planning to provide a summary of health care decision-making bodies internationally, and their stated requirements regarding the valuation of health states.

Detailed information regarding the valuation protocols, guidelines on which value set to use and tables of all available value sets has recently been published by Springer in: EuroQoL Group Monograph series: Volume 2: EQ-5D value sets: inventory, comparative review and user guide' (see section 8 for more information). Chapter 4 by Nancy Devlin and David Parkin will be of special interest to researchers pondering the issue of which value set to use.

8. Additional information

Key EuroQol references

1. The EuroQol Group (1990). EuroQol-a new facility for the measurement of health-related quality of life. Health Policy 16(3):199-208.

2. Brooks R (1996). EuroQol: the current state of play. Health Policy 37(1):53-72.

3. Dolan P (1997). Modeling valuations for EuroQol health states. Med Care 35(11):1095-108.

4. Roset M, Badia X, Mayo NE (1999). Sample size calculations in studies using the EuroQol 5D. Qual Life Res 8(6):539-49.

5. Greiner W, Weijnen T, Nieuwenhuizen M, et al. (2003). A single European currency for EQ-5D health states. Results from a six country study. Eur J Health Econ; 4(3):222-231.

6. Shaw JW, Johnson JA, Coons SJ (2005). US valuation of the EQ-5D health states: development and testing of the D1 valuation model. Med Care; 43(3): 203-220.

Referring to the EQ-5D instrument in publications

When publishing results obtained with the EQ-5D, the following references can be used:

1. The EuroQol Group (1990). EuroQol-a new facility for the measurement of health-related quality of life. Health Policy 16(3):199-208.

2. Brooks R (1996). EuroQol: the current state of play. Health Policy 37(1):53-72.

If you used a value set in your study you can also include a reference to the publication regarding that value set. The appropriate references for the value sets can be found in the EQ-5D Value Sets Monograph and in the value set summary documents that can be ordered from the EuroQoL Executive Office.

Products available from the EuroQoL Executive Office

EQ-5D language versions/guidelines for different modes of administration

All language versions and guidelines for different modes of administration must be obtained exclusively from the EuroQoL Executive Office. Normally only the language(s) appropriate to the country where the research request originates will be supplied. They are distributed freely provided the research is not being funded by a commercial organization (e.g. a pharmaceutical or medical device company). In these latter instances, sponsorship is requested.

The Measurement and valuation of health status using EQ-5D: A European perspective. Eds Brooks R, Rabin R, de Charro F. Kluwer Acacemic Publishers, 2005

This book reports on the results of the European Union-funded EQ-net project which furthered the development of EQ-5D in the key areas of valuation, application and translation. The book can be obtained from Springer at www.springeronline.com at a cost of €107.95.

Measuring self-reported population health: An international perspective based on EQ-5D. Eds Szende A, Williams A. EuroQoL Group Monographs Volume 1. SpringMed publishing, 2004.

This booklet provides population reference data for a number of different countries and is available on request from the EuroQoL Executive Office.

EQ-5D concepts and methods: a developmental history. Eds Kind P, Brooks R, Rabin R. Springer, 2005.

This book is a collection of papers representing the collective intellectual enterprise of the EuroQoL Group and can be obtained from Springer at www.springeronline.com at a cost of € 85.00.

EQ-5D value sets: Inventory, comparative review and user guide. Eds. Szende A, Oppe M, Devlin N. EuroQoL Group Monographs Volume 2. Springer, 2006.

This book provides an essential guide to the use of the EuroQoL Group's value sets for anyone working with EQ-5D data and can be obtained from Springer at www.springeronline.com at a cost of € 49.95.

Future developments

Since 2002, the EuroQoL Foundation has provided modest funding for EuroQoL members to carry out innovative EQ-5D-related research. Since 2004, the Group has been establishing specific task forces to:

- Investigate the use of EQ-5D in different disease areas
- Develop a 5-level version of EQ-5D
- Explore different valuation methodologies for the 5-level version
- Develop an EQ-5D version for children aged 7-12 years in different languages
- Investigate the use of EQ-5D in population health

- Explore the use of electronic versions of EQ-5D in pc and web-based applications as well as palm pilots and (in the future) cell phones. This task force will also investigate the eliciting of values via the computer

Contact information:

For more information please look at the EuroQoL website at www.euroqol.org or e-mail us at userinformationservice@euroqol.org

Acknowledgements:

Part of this user guide was taken from and is based on the UK user guide that was developed by Professor Paul Kind from York University, UK in 1998.

```
*Syntax EQ-5D

COMPUTE raw_ind = 97.66.

IF (GANG_F eq 2) raw_ind = raw_ind -5.78.

IF (GANG_F eq 3) raw_ind = raw_ind - 16.03.

IF (STELL_F eq 2) raw_ind = raw_ind - 10.28.

IF (STELL_F eq 3) raw_ind = raw_ind - 13.67.

IF (GJOREMAAL_F eq 2) raw_ind = raw_ind - 2.31.

IF (GJOREMAAL_F eq 3) raw_ind = raw_ind - 7.54.

IF (SMERTER_F eq 2) raw_ind = raw_ind - 8.15.

IF (SMERTER_F eq 3) raw_ind = raw_ind - 14.35.

IF (ANGST_F eq 2) raw_ind = raw_ind - 7.81.

IF (ANGST_F  eq 3) raw_ind = raw_ind - 11.31.

IF (GANG_F  ne 1 or GJOREMAAL_F ne 1 or STELL_F ne 1 or SMERTER_F ne 1 or ANGST_F ne 1)

 raw_ind = raw_ind - 11.21.

IF (GANG_F  eq 3 or STELL_F eq 3 or GJOREMAAL_F eq 3 or SMERTER_F eq 3 or ANGST_F eq 3)

 raw_ind = raw_ind - 20.06.

missing values GANG_F (8,9,99,999) STELL_F (8,9,99,999) GJOREMAAL_F (8,9,99,999)
SMERTER_F(8,9,99,999) ANGST_F (8,9,99,999).
```

```
IF (missing(GANG_F ) or missing(GJOREMAAL_F) or missing(STELL_F) or missing(SMERTER_F) or missing(ANGST_F)) raw_ind = 999.

missing values raw_ind (999).



COMPUTE VAS_Findex = 100 * (raw_ind - 10) / (97.66 - 10).

IF (missing(raw_ind)) VASindex = 999.

missing values VASindex (999).

EXECUTE.

COMPUTE raw_ind = 97.66.

IF (GANG_E eq 2) raw_ind = raw_ind -5.78.

IF (GANG_E eq 3) raw_ind = raw_ind - 16.03.

IF (STELL_E eq 2) raw_ind = raw_ind - 10.28.

IF (STELL_E eq 3) raw_ind = raw_ind - 13.67.

IF (GJOREMAAL_E eq 2) raw_ind = raw_ind - 2.31.

IF (GJOREMAAL_E eq 3) raw_ind = raw_ind - 7.54.

IF (SMERTER_E eq 2) raw_ind = raw_ind - 8.15.

IF (SMERTER_E eq 3) raw_ind = raw_ind - 14.35.

IF (ANGST_E eq 2) raw_ind = raw_ind - 7.81.

IF (ANGST_E  eq 3) raw_ind = raw_ind - 11.31.
```

```
IF (GANG_E  ne 1 or GJOREMAAL_E ne 1 or STELL_E ne 1 or SMERTER_E ne 1 or ANGST_E ne 1)

 raw_ind = raw_ind - 11.21.


IF (GANG_E  eq 3 or STELL_E eq 3 or GJOREMAAL_E eq 3 or SMERTER_E eq 3 or ANGST_E eq 3)

 raw_ind = raw_ind - 20.06.


missing values GANG_E (8,9,99,999) STELL_E (8,9,99,999) GJOREMAAL_E (8,9,99,999)
SMERTER_E(8,9,99,999) ANGST_E (8,9,99,999).


IF (missing(GANG_E ) or missing(GJOREMAAL_E) or missing(STELL_E) or missing(SMERTER_E) or
missing(ANGST_E)) raw_ind = 999.

missing values raw_ind (999).


COMPUTE VAS_Eindex = 100 * (raw_ind - 10) / (97.66 - 10).

IF (missing(raw_ind)) VASEindex = 999.

missing values VASEindex (999).


EXECUTE.
```

KOOS – Spørreskjema for knepasienter.

DATO: _____

FØDSELSNR (11 siffer): _____

NAVN: _____

SYKEHUS:_____

KRYSS AV FOR RIKTIG KNE : ☐ **VENSTRE**

(NB. Et skjema for **hvert** kne) ☐ **HØYRE**

Veiledning: Dette spørreskjemaet inneholder spørsmål om hvordan du opplever kneet ditt. Informasjonen vil hjelpe oss til å følge med i hvordan du har det og fungerer i ditt daglige liv. Besvar spørsmålene ved å krysse av for det alternativ du synes passer best for deg (kun ett kryss ved hvert spørsmål). Hvis du er usikker, kryss likevel av for det alternativet som føles mest riktig.

Symptom

Tenk på de **symptomene** du har hatt fra kneet ditt den **siste uken** når du besvarer disse spørsmålene.

S1. Har kneet vært hovent?

Aldri	Sjelden	I blant	Ofte	Alltid
☐0	☐1	☐2	☐3	☐4

S2. Har du følt knirking, hørt klikking eller andre lyder fra kneet?

Aldri	Sjelden	I blant	Ofte	Alltid
☐0	☐1	☐2	☐3	☐4

S3. Har kneet haket seg opp eller låst seg?

Aldri	Sjelden	I blant	Ofte	Alltid
☐0	☐1	☐2	☐3	☐4

S4. Har du kunnet rette kneet helt ut?

Alltid	Ofte	I blant	Sjelden	Aldri
☐0	☐1	☐2	☐3	☐4

S5. Har du kunnet bøye kneet helt?

Alltid	Ofte	I blant	Sjelden	Aldri
☐0	☐1	☐2	☐3	☐4

Stivhet

De neste spørsmålene handler om **leddstivhet** . Leddstivhet innebærer vanskeligheter med å komme i gang eller økt motstand når du bøyer eller strekker kneet. Marker graden av leddstivhet du har opplevd i kneet ditt den **siste uken**

S6. Hvor stivt er kneet ditt når du nettopp har våknet om morgenen?

Ikke noe	Litt	Moderat	Betydelig	Ekstremt
☐0	☐1	☐2	☐3	☐4

S7. Hvor stivt er kneet ditt **senere på dagen** etter å ha sittet, ligget eller hvilt?

Ikke noe	Litt	Moderat	Betydelig	Ekstremt
☐0	☐1	☐2	☐3	☐4

Smerte

P1. Hvor ofte har du vondt i kneet?

Aldri	Månedlig	Ukentlig	Daglig	Hele tiden
☐0	☐1	☐2	☐3	☐4

Hvilken grad av smerte har du hatt i kneet ditt den **siste uken** ved følgende aktiviteter?

P2. Snu/vende på belastet kne

Ingen	Lett	Moderat	Betydelig	Svært stor
☐0	☐1	☐2	☐3	☐4

P3. Rette kneet helt ut

Ingen	Lett	Moderat	Betydelig	Svært stor
☐0	☐1	☐2	☐3	☐4

P4. Bøye kneet helt

Ingen	Lett	Moderat	Betydelig	Svært stor
☐0	☐1	☐2	☐3	☐4

P5.Gå på flatt underlag

Ingen	Lett	Moderat	Betydelig	Svært stor
☐0	☐1	☐2	☐3	☐4

P6. Gå opp eller ned trapper

Ingen	Lett	Moderat	Betydelig	Svært stor
☐0	☐1	☐2	☐3	☐4

P7. Om natten i sengen (smerter som forstyrrer søvnen)

Ingen	Lett	Moderat	Betydelig	Svært stor
☐0	☐1	☐2	☐3	☐4

P8. Sittende eller liggende

Ingen	Lett	Moderat	Betydelig	Svært stor
☐0	☐1	☐2	☐3	☐4

P9. Stående

Ingen	Lett	Moderat	Betydelig	Svært stor
☐0	☐1	☐2	☐3	☐4

Funksjon i hverdagen

De neste spørsmål handler om din fysiske funksjon. **Angi graden av vanskeligheter du har opplevd den siste uken ved følgende aktiviteter på grunn av dine kneproblemer.**

A1. Gå ned trapper

Ingen	Lett	Moderat	Betydelig	Svært stor
☐0	☐1	☐2	☐3	☐4

A2. Gå opp trapper

Ingen	Lett	Moderat	Betydelig	Svært stor
☐0	☐1	☐2	☐3	☐4

Angi graden av **vanskeligheter** du har opplevd ved hver aktivitet den **siste uken.**

A3. Reise deg fra sittende stilling

Ingen	Lett	Moderat	Betydelig	Svært stor
☐0	☐1	☐2	☐3	☐4

A4. Stå stille

Ingen	Lett	Moderat	Betydelig	Svært stor
☐0	☐1	☐2	☐3	☐4

A5. Bøye deg, f.eks. for å plukke opp en gjenstand fra gulvet

Ingen	Lett	Moderat	Betydelig	Svært stor
☐0	☐1	☐2	☐3	☐4

A6. Gå på flatt underlag

Ingen	Lett	Moderat	Betydelig	Svært stor
☐0	☐1	☐2	☐3	☐4

A7. Gå inn/ut av bil

Ingen	Lett	Moderat	Betydelig	Svært stor
☐0	☐1	☐2	☐3	☐4

A8. Handle/gjøre innkjøp

Ingen	Lett	Moderat	Betydelig	Svært stor
☐0	☐1	☐2	☐3	☐4

A9. Ta på sokker/strømper

Ingen	Lett	Moderat	Betydelig	Svært stor
☐0	☐1	☐2	☐3	☐4

A10. Stå opp fra sengen

Ingen	Lett	Moderat	Betydelig	Svært stor
☐0	☐1	☐2	☐3	☐4

A11. Ta av sokker/strømper

Ingen	Lett	Moderat	Betydelig	Svært stor
☐0	☐1	☐2	☐3	☐4

A12. Ligge i sengen (snu deg, holde kneet i samme stilling i lengre tid)

Ingen	Lett	Moderat	Betydelig	Svært stor
☐0	☐1	☐2	☐3	☐4

A13. Gå inn og ut av badekar/dusj

Ingen	Lett	Moderat	Betydelig	Svært stor
☐0	☐1	☐2	☐3	☐4

A14. Sitte

Ingen	Lett	Moderat	Betydelig	Svært stor
☐0	☐1	☐2	☐3	☐4

A15. Sette deg og reise deg fra toalettet

Ingen	Lett	Moderat	Betydelig	Svært stor
☐0	☐1	☐2	☐3	☐4

Angi graden av **vanskeligheter** du har opplevd ved hver aktivitet den **siste uken.**

A16. Gjøre tungt husarbeid (måke snø, vaske gulv, støvsuge osv.)

Ingen	Lett	Moderat	Betydelig	Svært stor
☐0	☐1	☐2	☐3	☐4

A17. Gjøre lett husarbeid (lage mat, tørke støv osv.)

Ingen	Lett	Moderat	Betydelig	Svært stor
☐0	☐1	☐2	☐3	☐4

Funksjon, sport og fritid

De neste spørsmålene handler om din fysiske funksjon. **Angi graden av vanskeligheter du har opplevd den siste uken ved følgende aktiviteter på grunn av dine kneproblemer.**

SP1. Sitte på huk

Ingen	Lett	Moderat	Betydelig	Svært stor
☐0	☐1	☐2	☐3	☐4

SP2. Løpe

Ingen	Lett	Moderat	Betydelig	Svært stor
☐0	☐1	☐2	☐3	☐4

SP3. Hoppe

Ingen	Lett	Moderat	Betydelig	Svært stor
☐0	☐1	☐2	☐3	☐4

SP4. Snu/vende på belastet kne

Ingen	Lett	Moderat	Betydelig	Svært stor
☐0	☐1	☐2	☐3	☐4

SP5. Stå på kne

Ingen	Lett	Moderat	Betydelig	Svært stor
☐0	☐1	☐2	☐3	☐4

Livskvalitet

Q1. Hvor ofte gjør ditt kneproblem seg bemerket?

Aldri	Månedlig	Ukentlig	Daglig	Alltid
☐0	☐1	☐2	☐3	☐4

Q2. Har du forandret levesett for å unngå å overbelaste kneet?

Ingenting	Noe	Moderat	Betydelig	Fullstendig
☐0	☐1	☐2	☐3	☐4

Q3. I hvor stor grad kan du stole på kneet ditt?

Fullstendig	I stor grad	Moderat	Til en viss grad	Ikke i det hele tatt
☐0	☐1	☐2	☐3	☐4

Q4. Generelt sett, hvor store problemer har du med kneet ditt?

Ingen	Lette	Moderate	Betydelige	Svært store
☐0	☐1	☐2	☐3	☐4

Takk for at du tok deg tid og besvarte samtlige spørsmål!

KOOS *Manual scoring sheet*

Instructions:
Assign the following scores to the boxes!

None	Mild	Moderate	Severe	Extreme
□	□	□	□	□
0	1	2	3	4

Missing data. If a mark is placed outside a box, the closest box is chosen. If two boxes are marked, that which indicated the more severe problems is chosen. Missing data are treated as such; one or two missing values are substituted with the average value for that subscale. If more than two items are omitted, the response is considered invalid and no subscale score is calculated.

Sum up the total score of each subscale and divide by the possible maximum score for the scale. Traditionally in orthopedics, 100 indicates no problems and 0 indicates extreme problems. The normalized score is transformed to meet this standard. Please use the formulas provided for each subscale!

1. PAIN $100 - \frac{\text{Total score P1-P9} \times 100}{36} = 100 - \frac{\_\_\_\_\_}{36} = \_\_\_\_\_$

2. SYMPTOMS $100 - \frac{\text{Total score S1-S7} \times 100}{28} = 100 - \frac{\_\_\_\_\_}{28} = \_\_\_\_\_$

3. ADL $100 - \frac{\text{Total score A1-A17} \times 100}{68} = 100 - \frac{\_\_\_\_\_}{68} = \_\_\_\_\_$

4. SPORT&REC $100 - \frac{\text{Total score SP1-SP5} \times 100}{20} = 100 - \frac{\_\_\_\_\_}{20} = \_\_\_\_\_$

5.QOL $100 - \frac{\text{Total score Q1-Q4} \times 100}{16} = 100 - \frac{\_\_\_\_\_}{16} = \_\_\_\_\_$

WOMAC *How to score from the KOOS*

Assign scores from 0 to 4 to the boxes as shown above. To get original WOMAC scores sum the item scores for each subscale. If you prefer percentage scores in accordance with the KOOS, use the formula provided below to convert the original WOMAC scores.

$$\text{Transformed scale} = 100 - \frac{\text{actual raw score} \times 100}{\text{Possible raw score range}}$$

WOMAC subscores	Original score = sum of the following items	Possible raw score range
Pain	P5-P9	20
Stiffness	S6-S7	8
Function	A1-A17	68

FORESPØRSEL OM DELTAKELSE I FORSKNINGSPROSJEKT
Profix kneprotese, konvensjonell vs computernavigert.

De skal opereres med en kneprotese. Dette er en etablert behandling med gode resultater for de aller fleste pasienter. Operasjonen innebærer at man setter inn et kunstig kneledd av plast og metall som festes med bensement. Som annen medisinsk behandling er også kneprotesekirurgien i stadig utvikling, og man forsøker hele tiden å finne løsninger som ytterligere vil bedre behandlingsresultatene. Som ledd i vår søken etter bedre løsninger vil vi nå sammenligne kneproteser operert med vanlig, standard metode og kneproteser operert ved hjelp av såkalt computernavigasjon.
Profix-protesen er den protesen som brukes som standard i Helse Vest og på Lovisenberg Diakonale Sykehus, og den har gode resultater.
Computernavigasjon har de siste 5-6 år kommet for fullt inn i protesekirurgien. I Norge er det få sykehus som tilbyr slik behandling. Man har foreløpig begrenset dokumentasjon på nytten av dette nye operasjonsverktøyet. Man bruker et infrarødt kamera som sender og mottar signaler under operasjonen. Signalene overføres fra kneet til en computer som lager en modell av kneet ditt. Ut ifra denne modellen foretas visse beregninger som hjelper kirurgen å plassere protesen riktig. Standardmetoden i dag er å beregne protesens plassering ved hjelp av en siktepinne som settes i marghulen og visse anatomiske landemerker. Vi vil undersøke hvilken metode som gir best resultat med tanke på riktig plassering av protesen, som igjen har betydning for hvor lenge protesen varer før den evt må skiftes ut. Vi vil også undersøke hvilken metode som gir minst sykelighet og komplikasjoner etter operasjonen. Funksjon og livskvalitet vil bli vurdert, også i et helseøkonomisk perspektiv.

De blir herved forespurt om De vil delta i en studie som har til hensikt å sammenligne behandlingsresultatet med disse to metodene.

Hva innebærer deltakelse i studien?

Studien innebærer at man ved loddtrekning velger hvilken metode pasienten skal opereres med. Plassering av reflektorkuler for computernavigering innebærer to små (1cm) hudsnitt på leggen. Kulene festes med pinner som skrues fast i benet. Begge grupper vil få dette hudsnittet. Oppfølgingen vil også være den samme uavhengig av metoden. Pasienter som deltar i studien, vil under operasjonen få satt inn små metallmarkører (0,8-1mm) av metallet tantal i benet rundt protesen og i plastkomponenten. Disse metallmarkørene har vært benyttet til dette formålet internasjonalt i flere tiår og har ingen påviste bivirkninger. Ved hjelp av markørene og helt spesielle røntgenbilder kan man påvise mikroskopisk bevegelse av protesedelene og slitasje av plasten. Grad av bevegelse og slitasje sier noe om protesens stabilitet og derved kvalitet. Pasienter som deltar i studien vil få en ekstra nøye oppfølging med røntgenundersøkelser etter 3, 12 og 24 måneder, samt vanlig rtg. kontroll og undersøkelse etter 5 og 10 år. Det vil dessuten bli foretatt en CT-kontroll av kneet 3 måneder etter operasjonen for å sjekke protesens plassering. Dette medfører en strålebelastning på 1 mSv som tilsvarer 3 røntgenbilder av bekkenet.

Håndtering av opplysninger og Personvern

Deltagelse er frivillig, og De kan trekke dem fra studien, også etter operasjon. Dersom De velger ikke å delta i studien, vil dette ikke ha noen innvirkning på Deres behandling ved sykehuset, og De vil bli operert på vanlig måte med en standard Profix kneprotese.

De opplysninger og data som framkommer gjennom studien vil samles og databehandles. Dataene tas fra din vanlige pasientjournal fra opphold ved innleggelse for operasjon, påfølgende rtg. og polikliniske kontroller hos lege og fysioterapeut. Vi registrerer plassering av protesen, bevegelse av protese, grad av smerte, funksjon, andre sykdommer, evt. bivirkninger og bruk av medikamenter. I tillegg vil fysioterapeuten evaluere opptreningsperioden med et eget spørreskjema. Studien er et samarbeidsprosjekt mellom Haugesund sjukehus, Haugesund sanitetsforenings revmatismesjukehus, Lovisenberg Diakonale Sykehus og Haukeland Universitetssykehus. Opplysninger om enkeltpasienters identitet vil bli oppbevart ved hvert behandlende sykehus, mens data samlet inn i prosjektet vil bli utvekslet mellom sykehusene i avidentifisert form. Alle opplysningene vil bli behandlet konfidensielt. Prosjektet avsluttes år 2017, etter 10 års oppfølging av alle pasienter, og alle innsamlede forskningsdata vil da anonymiseres. Vanlige journalopplysninger vil ikke slettes.

Studien er klarert av Regional komité for medisinsk forskningsetikk Vest-Norge og meldt til Personvernombudet for forskning, Norsk samfunnsvitenskapelig datatjeneste AS.

Studien ledes av Klinikkoverlege professor dr. med. Ove Furnes, ved Ortopedisk avd. Haukeland Universitetssykehus.

Spørsmål vedrørende studien kan rettes til din behandlende lege, eller til legen som er ansvarlig for studien ved det sykehuset hvor De behandles.

Vennlig hilsen

Klinikkoverlege professor dr. med. Ove Furnes
Haukeland Universitetssykehus

Overlege Øystein Gøthesen
Haugesund Sjukehus

Overlege Herman Luhr
Haugesund sanitetsforenings revmatismesjukehus

Avdelingsoverlege Øystein Høvik
Lovisenberg Diakonale Sykehus

INFORMERT SAMTYKKE

Undertegnede har lest den vedlagte informasjonen og har diskutert studien med ansvarlig lege. Jeg er villig til å delta i studien.

_____	_____
Pasientsignatur	**Dato:** **(Pasienten skriver selv dato)**

Som ansvarlig lege bekrefter jeg at pasienten har fått muntlig og skriftlig informasjon om studien, og at pasienten har signert samtykke før prosjektspesifikke undersøkelser eller prosedyrer er påbegynt.

_____	_____
Ansvarlig leges signatur	**Dato:**

Revidert 2.august, 2010

Protocol - alignment and position

All angles are measured from the lateral side (coronal (frontal) view) or posteriorly (sagittal view).
All images in this protocol are from a right side knee.

Part 1. Computer tomography scans
Part 2. Full-length standing radiographs

Part 1. Computer tomography scans – method and definitions

Timing:
Performed at 3 months follow-up

Equipment:
A multi-slice scanner (64 slices) was used at 3 months follow-up at all hospitals involved in the trial, and the tomography was performed according to the Perth protocol [1].
Software for measurements of alignment: IMPAX Agfa version 6.4.0.4551. The images are analyzed using two computer screens facilitating cross-bearing in three dimensions, and data are registered directly into the database.

Positioning:

Patient in a supine position with toes pointing towards the roof. Ankles placed in a neutral position. Forefeet supported by taping/support if needed, to avoid outward rotation of the legs.

Definitions:

Mechanical axes of the knee replaced limb[2-4]:
Femur - coronal view: Axis from centre of hip to centre of femoral component
Femur - sagittal view: Axis from centre of hip to rotational centre of femoral component
Tibia - coronal and sagittal view: Axis from centre of tibial component to centre of ankle
Limb - coronal view: Femoral axis + Tibial axis

Centre of joints:
General principle: cross-bearing in three dimensions (Fig.A)

Hip:
Draw a circle to find centre of the femoral head (Fig.A1/A4)

Knee/Femoral component:
Coronal view: Point (on the joint line) where a perpendicular of the condylar tangent points towards the deepest part of the intercondylar groove (Fig.A2).
Sagittal view: Point (on the joint line) where a perpendicular of the condylar tangent points towards the deepest part of the intercondylar groove (Fig.A3).
Axial view: Mid-point of a line between the anterior faces of the pegs (Fig A8).

Centre of rotation/sagittal view: Draw circles to find a) the centre of the anterior part of the medial condyle, and b) the centre of the posterior part of the medial condyle (a typical J-shaped articulation). Centre of rotation of the knee is defined as the mid-point between these centres.(Fig.B)

Knee/Tibial component:
Coronal view: Mid-point of longest line from lateral to medial (Fig.C1).
Sagittal view: A line parallel and posterior to the stem crosses the upper surface of the tibial component. This crossing is defined as centre of the tibial component (Fig.C2).
Axial view: Mid-point of longest line from lateral to medial, crossing the centres of two oval shaped joint surfaces of the tibial component (Fig.C3).

Ankle (Fig.D):
Coronal view:
Middle of the ankle is defined as the mid-point of a line on the talus from medial to lateral.
Sagittal view:
Mid-point of the talar dome. (If the ankle is plantarly flexed, use the mid-point of the distal tibial joint surface)
Axial view:
Mid-point of a line from medial to lateral talar body.

Measures: Alignment and position of the implant:

1. Alfa1 (α1, Fig.E1): Alignment of the femoral component in the coronal view, referring to the mechanical axis of the "new" femur.
    a. The line between the pegs, adjusted with the tangent of the condyles, defines the line of the implant. This line is measured against the mechanical axis of the femur.
2. Beta1 (β1, Fig.E2): Alignment of the tibial component in the coronal view, referring to the mechanical axis of the "new" tibia.
    a. A line parallel to the upper surface of the tibial component, adjusted with a perpendicular line parallel to the stem, defines the line of the implant. This line is measured against the mechanical axis of the tibia.
3. Gamma (γ, Fig.E3): Alignment of the femoral component in the sagittal view, referring to the mechanical axis of the "new" femur.
    a. The mechanical axis in the sagittal plane is defined as the axis from the centre of the hip to the rotational centre of the femoral component. A line drawn parallel to the pegs adjusted by any of the backsides of the femoral component, defines the line of the implant. This line is measured against the mechanical axis of the femur.
4. Sigma (σ, Fig.E4): Alignment of the tibial component in the sagittal view, referring to the mechanical axis of the "new" tibia.
    a. A line parallel to the upper surface of the tibial component, adjusted with a perpendicular line parallel to the stem, defines the line of the implant. This line is measured against the mechanical axis of the tibia.
5. Lambda (λ, Fig.E5): The rotational position of the femoral component relative to the trans-epicondylar line. A line parallel to the posterior condyles, adjusted by a line between the pegs, defines the line of the implant. The perpendicular of this line is measured against the trans-epicondylar axis. The trans-epicondylar axis is drawn from

the most prominent part of the lateral epicondyle to the deepest point of the groove between the insertion of the superficial and the deep medial collateral ligament. (In cases with no groove, the most prominent part of the medial epicondyle is chosen as the reference point).

6. Mu (μ, Fig.E6): The rotational position of the tibial component relative to the anterior posterior axis (AP-axis). A line parallel to the posterior condyles defines the line of the implant. The AP- axis is defined as a line drawn from a point marking 1/3 of the medial tibial tubercle to a point representing the insertion of the posterior cruciate ligament. A CT slice where an S-shape is found at the back of the tibia is chosen, and the posterior point is marked where the concavity of the S turns into convexity.
7. Omega (ω, Fig.E7): The line of the femoral component in Lambda (λ) is superimposed on the line of the tibial component in Mu (μ). The angle between the two components represent a match/mismatch. Ideally this angle should be 10°, since the tibial component of the Profix prosthesis is supposed to be positioned in 10° internal rotation to achieve good bone coverage. (The polyethylene joint surface is externally rotated 10° to neutralize the rotation of the tibial component. Then the match between the polyethylene joint surface and the femoral component is zero degrees (perfect match)).
8. Chi1 (χ1), Hip-Knee-Ankle (HKA) angle: Alfa1 + Beta1

Part 2. Full-length standing radiographs

Timing:

Performed preoperatively and at 3 months follow-up.

Positioning:

Patient standing with toes pointing in a straight forward direction and the knees in full extension

Definitions:

Mechanical axis of femur: Centre of hip to centre of prosthetic knee
Mechanical axis of tibia: Centre of prosthetic knee to centre of ankle

Centre of preoperative (native) knee (Figure F): A point between centre of femoral notch and tibial spines is extrapolated perpendicularly down to the joint line [5].

Centre of hip: Circles are used to identify the centre of rotation of the hip (Fig.G)
Centre of the prosthetic knee: A perpendicular of the femoral condylar tangent pointing to the deepest point of the intercondylar groove. The crossing of the perpendicular line and the tangent defines the prosthetic centre (Fig.G)
Centre of the ankle: Centre of a line from medial to lateral talar body (Fig.G)

Measures:

Alignment of the prosthetic knee

1. Chi2 ($\chi 2$), Hip-Knee-Ankle (HKA) angle: Angle between mechanical axes of femur and tibia (Fig.G)
2. Alfa2 ($\alpha 2$), Alignment of the femoral component: Angle between femoral condylar joint line and mechanical axis of the femur (Fig.H1)
3. Beta2 ($\beta 2$), Alignment of the tibial component: Angle between femoral condylar joint line and mechanical axis of the tibia (Fig.H2)

Alignment of the preoperative (native) knee (Fig.G)

4. Chi0 ($\chi 0$), HKA-angle: Angle between mechanical axes of native femur and native tibia.

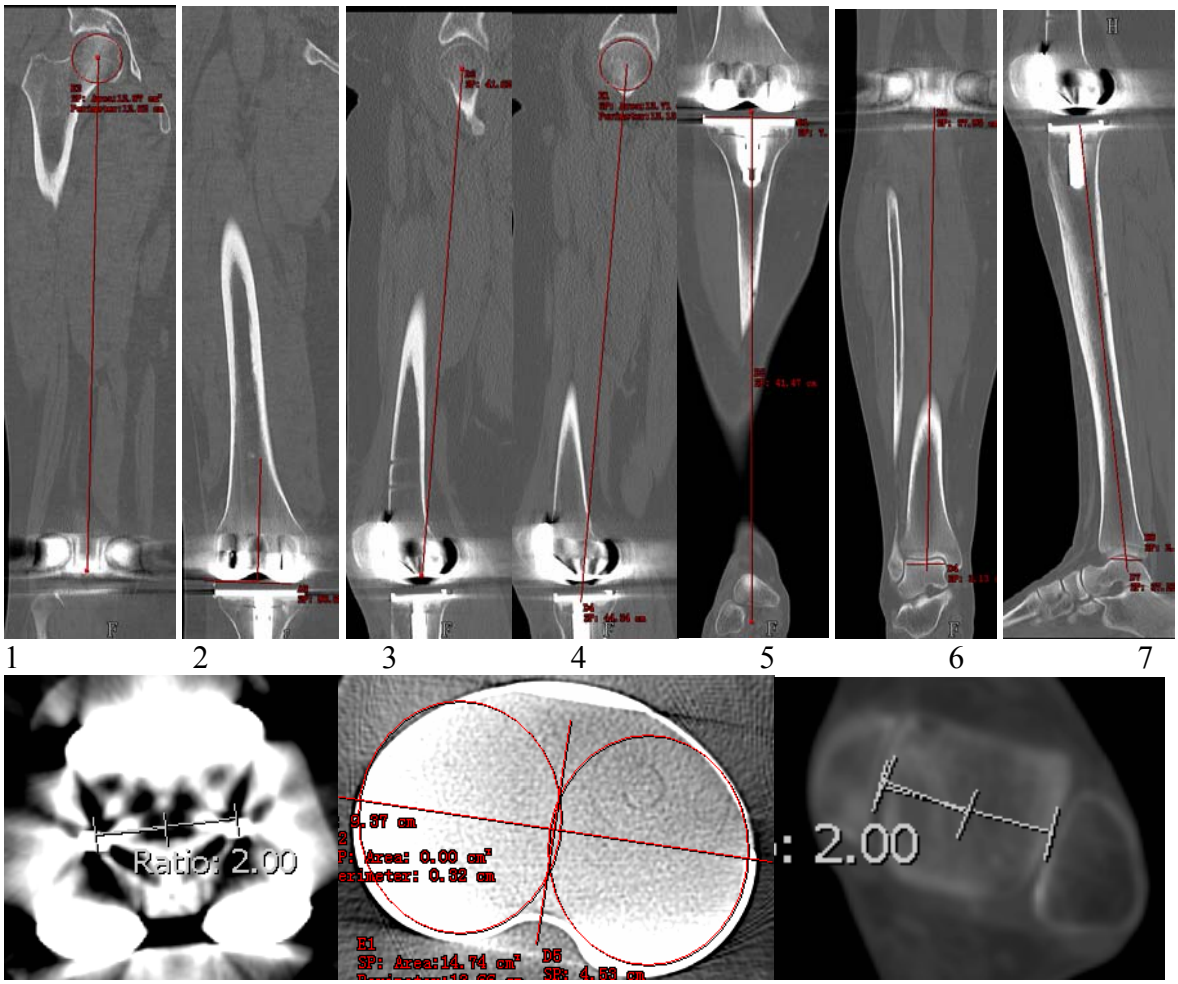


Figure A 1-10. Showing cross-bearing of coronal, sagittal and axial views to find mechanical axes of the prosthetic femur and tibia.

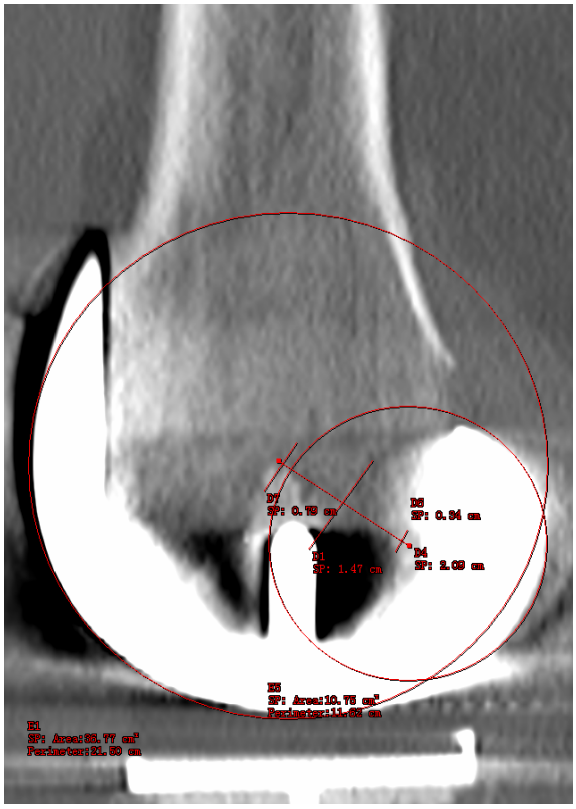
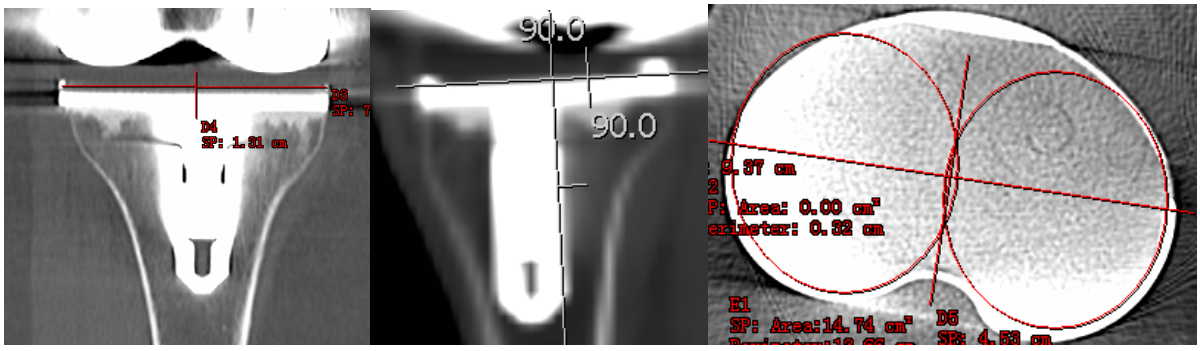
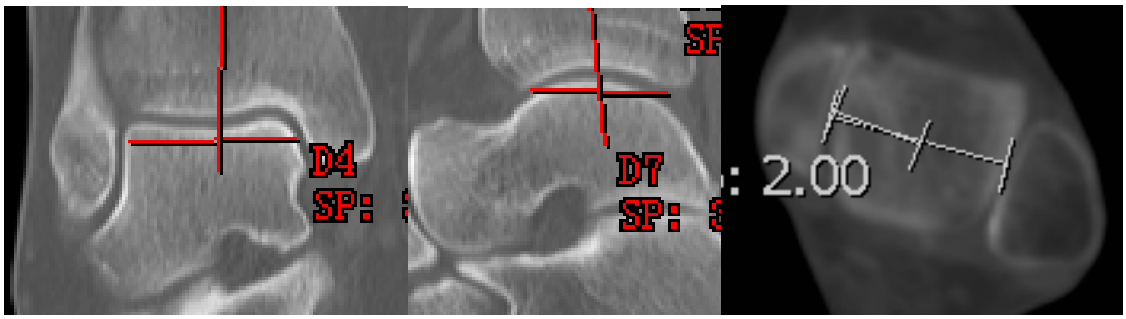


Figure B. Centre of rotation of the femoral component[6].



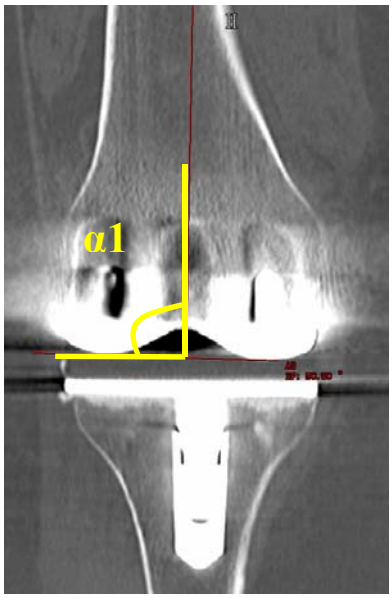
1 2 3

Figure C. The stem is somewhat medialized in the Profix tibia component, thus the centre of the component is somewhat lateral to the centre of the stem.

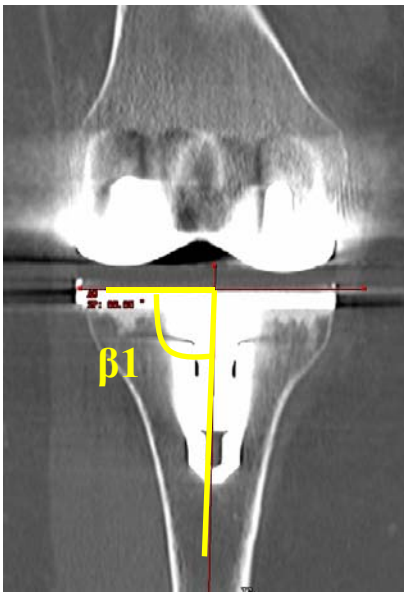


1 2 3

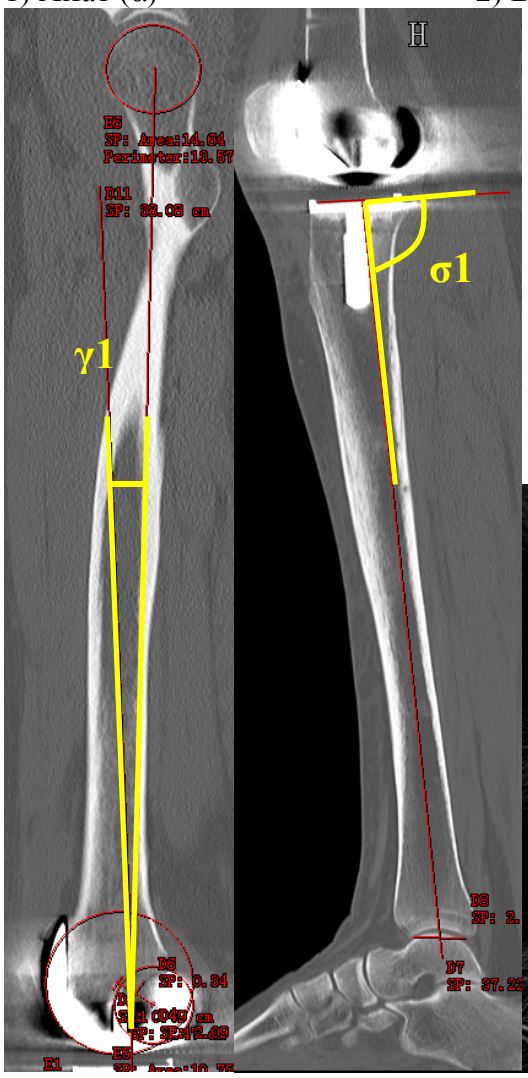
Figure D. Centre of the ankle in coronal (1), sagittal (2) and axial (3) views.



1) Alfa1 (α)

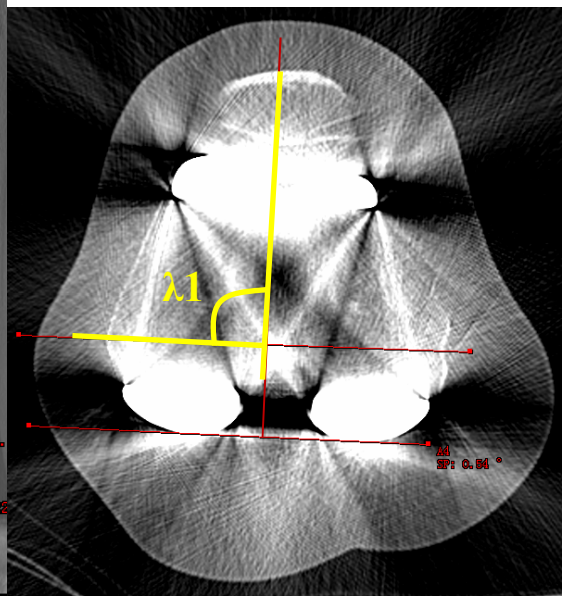


2) Beta1 (β)

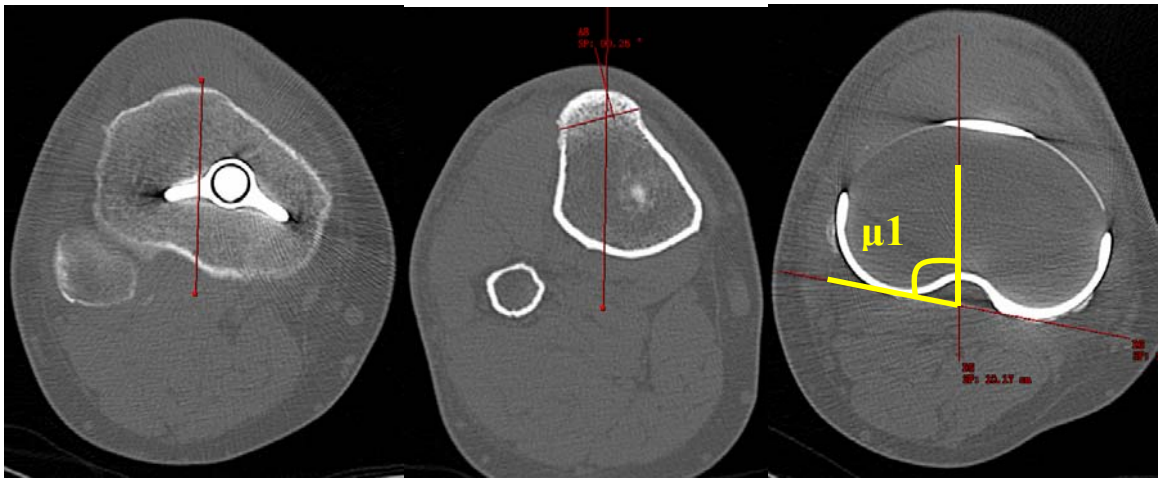


3) Gamma1 (γ)

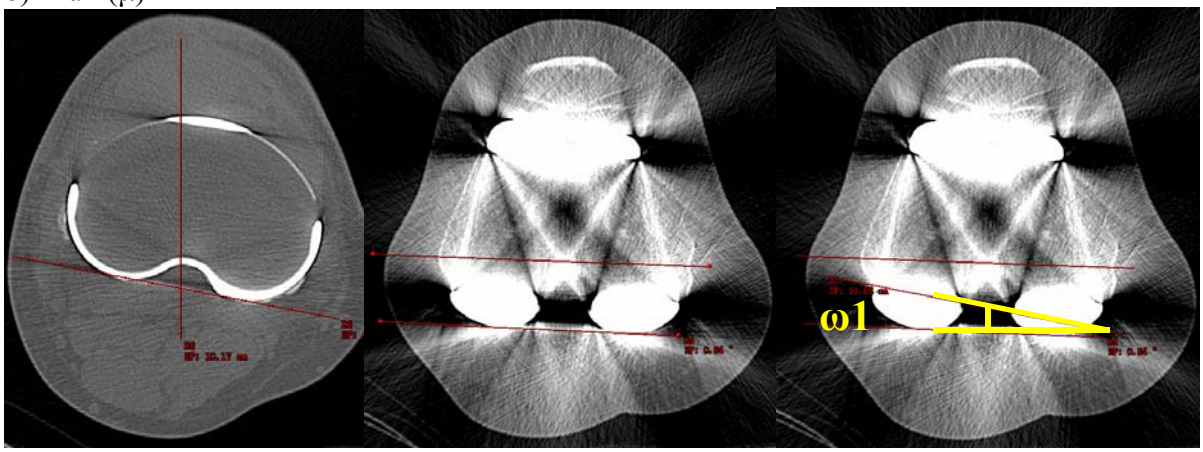
4) Sigma1 (σ)



5) Lamda1 (λ)



6) Mu1 (μ)



7) Omega1 (ω)

Figure E.1-7. Measuring the angles: alfa, beta, gamma, sigma, lambda, mu, and omega.

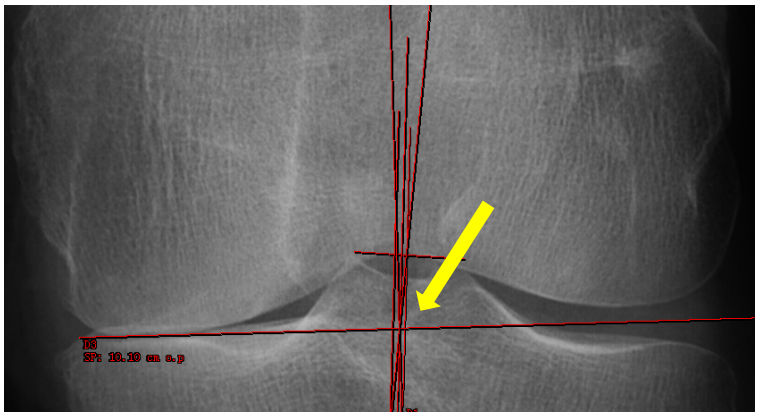


Figure F. Yellow arrow shows the centre of the native knee. A point between the centre of the femoral notch and the tibial spines is extrapolated perpendicularly down to the joint line.

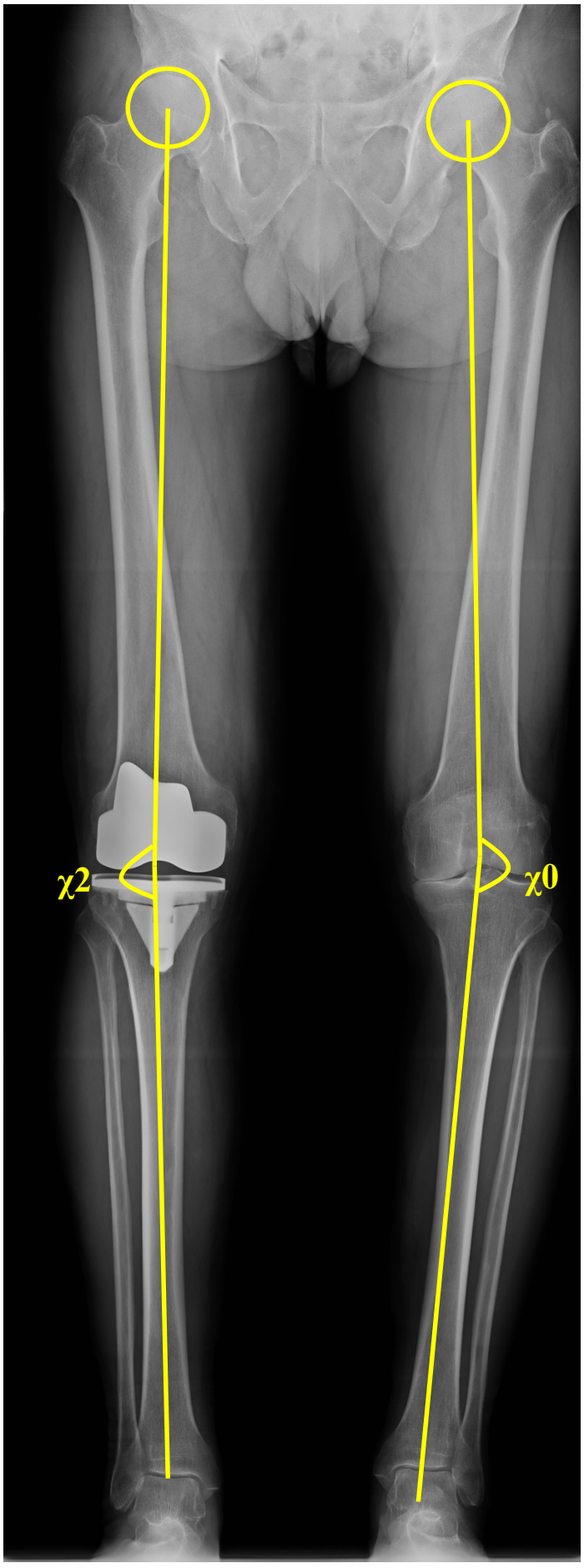
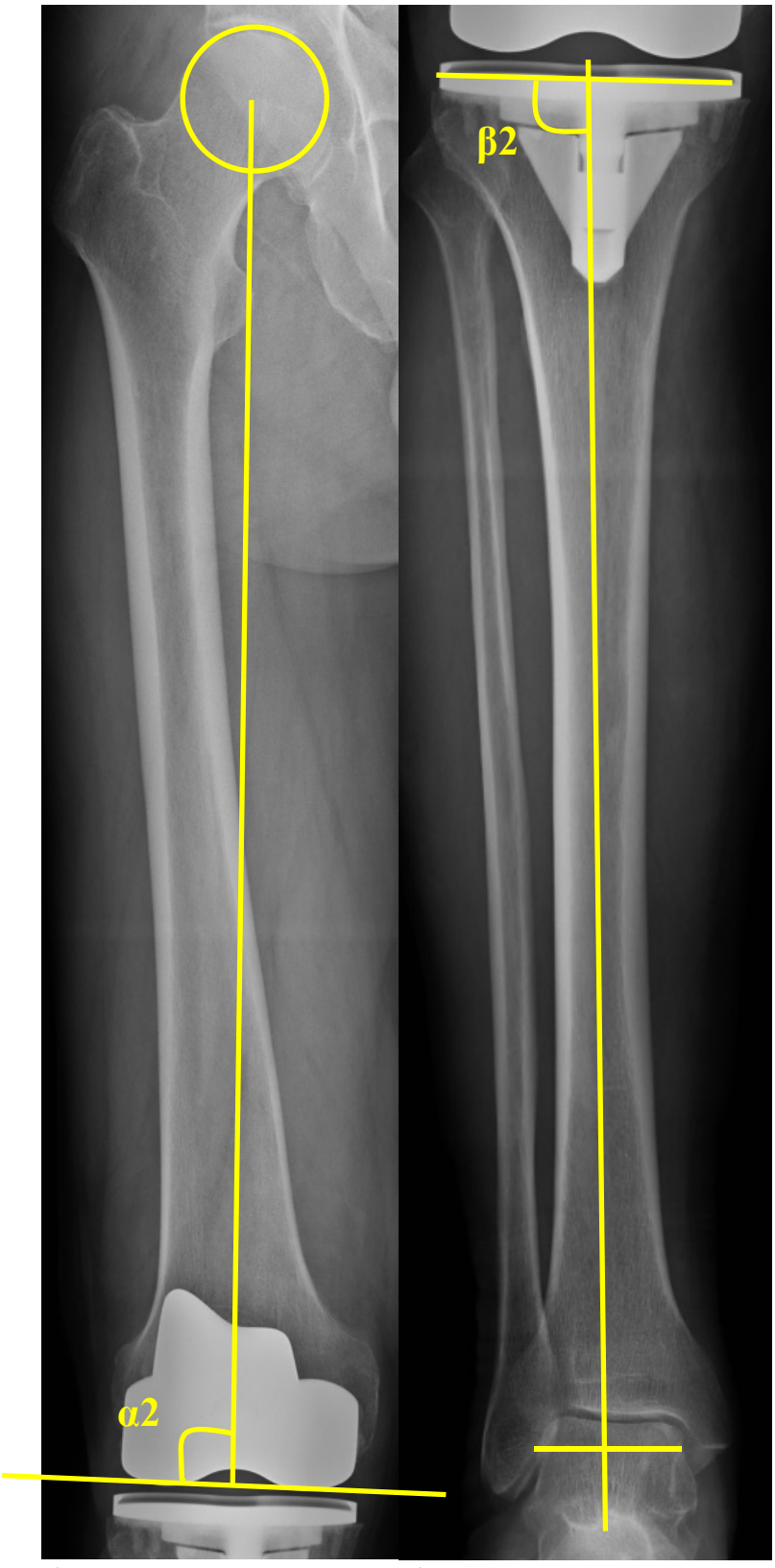


Figure G. The Hip-Knee-Ankle angle on full-length radiographs of a prosthetic knee (χ2) and a non-operated/native knee (χ0).



1) 2)

Figure H1-2. Alignment of the femoral component (α2) and the tibial component (β2) on full-length radiographs.

Reference List

(1) Chauhan SK, Clark GW, Lloyd S, Scott RG, Breidahl W, Sikorski JM. Computer-assisted total knee replacement. A controlled cadaver study using a multi-parameter quantitative CT assessment of alignment (the Perth CT Protocol). *J Bone Joint Surg Br* 2004; 86(6):818-823.

(2) Matziolis G, Krocker D, Weiss U, Tohtz S, Perka C. A prospective, randomized study of computer-assisted and conventional total knee arthroplasty. Three-dimensional evaluation of implant alignment and rotation. *J Bone Joint Surg Am* 2007; 89(2):236-243.

(3) Paley D, Herzenberg JE, Tetsworth K, McKie J, Bhave A. Deformity planning for frontal and sagittal plane corrective osteotomies. *Orthop Clin North Am* 1994; 25(3):425-465.

(4) Paley D, Pfeil J. [Principles of deformity correction around the knee]. *Orthopade* 2000; 29(1):18-38.

(5) Moreland JR, Bassett LW, Hanker GJ. Radiographic analysis of the axial alignment of the lower extremity. *J Bone Joint Surg Am* 1987; 69(5):745-749.

(6) The influence of femoral component position and tibial posterior slope on knee stability and range of motion after total knee arthroplasty. 70th Annual Meeting American Academy of Orthopaedic Surgeons; 03 Feb 13; 2003.

Randomization procedure

Patients are randomly parallel-group assigned to CAS or CONV (allocation ratio 1:1).

Separate randomization lists are created for each surgeon participating in the study using the statistical software PASW Statistics v 19 (IBM SPSS, Armonk, New York).

Block randomization with randomly varying block sizes of 2 and 4 is generated to achieve approximate equal numbers in the treatment groups at all times.

A central randomization office performs computer-generated allocation to trial group, with concealment by identical, opaque, sequentially numbered, sealed envelopes.

An investigator with no clinical involvement in the trial performs the randomization, and sequentially numbered envelopes are sent to an independent local contact/research assistant.

Initially 10 envelopes per surgeon are sent to the research assistant at the hospital.

The research assistant orders 10 more envelopes when needed, from the central randomization office.

When a patient has given consent to participate in the trial, the research assistant is given notice.

The envelope is opened as close to the operation as possible (normally the day before surgery), by the research assistant, who informs the surgeon about the result of the allocation assignment.

The randomization form is dated and the name of the patient is written on the form before filing.

A 4-digit number is given to all patients:

The first digit refers to the hospital; Haugesund (1), Haukeland (2) and Lovisenberg (3)

The second digit refers to the surgeon; Gøthesen (11), Luhr (12), Skredderstuen (21), Furnes (22), Hallan (23), Jacobsen (24), Petursson (31), Uppheim (32), Jervidalo (33).

The two last digits refer to the patient; i.e. the third patient of Gøthesen's is number 1103 and the fourteenth patient is number 1114.

PASIENTSKJEMA;

Computernavigasjon vs konvensjonell metode v/TKA.

⇨ **Pasientnummer:…….**

⇨ **Fødselsdato:.....**

⇨ **Kjønn: Mann____Kvinne___**(sett kryss)

⇨ **Diagnose:**

1. Primær gonartrose
2. Sequele fraktur
3. RA
4. Psoriasis / Bechterev
5. Annet. Presiser:…….

⇨ **Side:** Hø
Ve

⇨ **Charnley klasse:**

A -Unilateral knelidelse
B -Bilateral knelidelse
C -Multippel leddlidelse eller annen sykdom som nedsetter gangfunksjonen

⇨ **Status i kontralaterale kne:**

1. Normal funksjon
2. Moderat nedsatt funksjon
3. Alvorlig nedsatt funksjon

⇨ **Tidligere inngrep i aktuelle kne:**

1. Åpen/Artroskopisk meniskreseksjon/debridement
   a. 0-1 år siden
   b. >1 år siden
2. Osteosyntese etter fraktur:
   a. Patella
   b. Femur
   c. Tibia
   d. Kombinasjon av ovennevnte
3. Artroskopisk båndoperasjon
   a. ACL
   b. Annet (inkl pcl, mcl, lcl, menisksutur etc)

⇨ **Tidligere sykdommer:**

1. DVT i aktuelle underekstremitet
2. DVT i kontralaterale underekstremitet
3. Lungeemboli
4. Hjerteinfarkt
5. Atrieflimmer/flutter
6. Annen hjerterytmeforstyrrelse
7. Hjerteklaff-sykdom
8. TIA
9. Sequele etter hjerneslag/hjerneblødning
10. Revmatoid artritt
11. Psoriasis artritt
12. Polyartritt

⇨ **Allergier: penicillinallergi: Ja___Nei___**

⇨ **Medikamenter:**

Medikament	Dose (vedlikeholds-)	Sluttdato preop	Gjenoppstarts -dato postop	Pågående (ikke seponert preop – sett kryss)
1. Marevan	mg pr uke			
2. Albyl-E	mg pr dag			
3. Plavix	mg pr dag			
4. Ticlid	mg pr dag			
5. Persantin	mg pr dag			
6. **Annet antitrombotikum**	mg pr dag			

⇨ **Høyde (cm):_____**

⇨ **Vekt (kg):_____**

⇨ **Blodprøver:**

Preoperativt: Hb_____
Hct____
Postoperativt dag 2-3: Hb_____
Hct____

⇨ **Transfusjoner (totalt antall enheter a 250ml):_____**

⇨ **Operasjonsdato:**

⇨ **Operatør:**

⇨ **Blodtomhetstid (min):_____**

⇨ **Knivtid (min):_____**

⇨ **Anestesitype/postop sm.regime:**

1. **Spinal/epidural**
2. **Narkose/annet**

⇨ **Komplikasjoner/bivirkninger:**

1. Dyp infeksjon
2. DVT
3. Lungeemboli
4. Hjerteinfarkt
5. Hjerneslag
6. Fraktur
7. Utstyrssvikt (spesifiser!)
8. Annet

Signatur, ansvarlig lege……

Dato:……