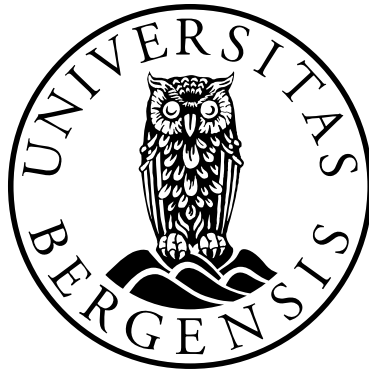


# Computer Navigation in Total Knee Replacement Surgery

*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.

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**ACKNOWLEDGEMENTS**

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## 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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Geir Hallan (Orthopedic Surgeon, MD/PhD),

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Peter Ellison (Post-Doc Research Fellow at Laboratory of Bio-materials, PhD),

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Jan Erik Askildsen (Professor, Health Economics, PhD),

Henrik Malchau (Professor, Orthopedic Surgeon, MD/PhD),

James Slover (Assistant Professor, MD/PhD).

## 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 Sørbo (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*

Gøthesen, 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*

Gøthesen, 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*

Gøthesen, 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*

Gøthesen, 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<sup>1</sup>. 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<sup>2-4</sup>. 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<sup>1</sup>. 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<sup>5-8</sup>. 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<sup>9,10</sup>.

Computer assisted surgery (CAS) was first introduced to neurosurgery<sup>11</sup> and then later to orthopedic surgery and knee replacement<sup>12,13</sup>. 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<sup>14</sup>. There were concerns about increased costs and operating times, and

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

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 adaptations, 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<sup>20</sup>. The impact of CAS on rotational alignment is still debated as the results are divergent<sup>14;21;22</sup>. Most trials with CAS report no improvement in functional results<sup>23;24</sup>. 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<sup>25</sup>, 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).

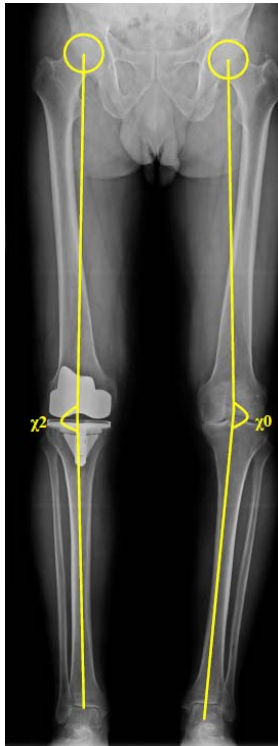


Fig. 1a)

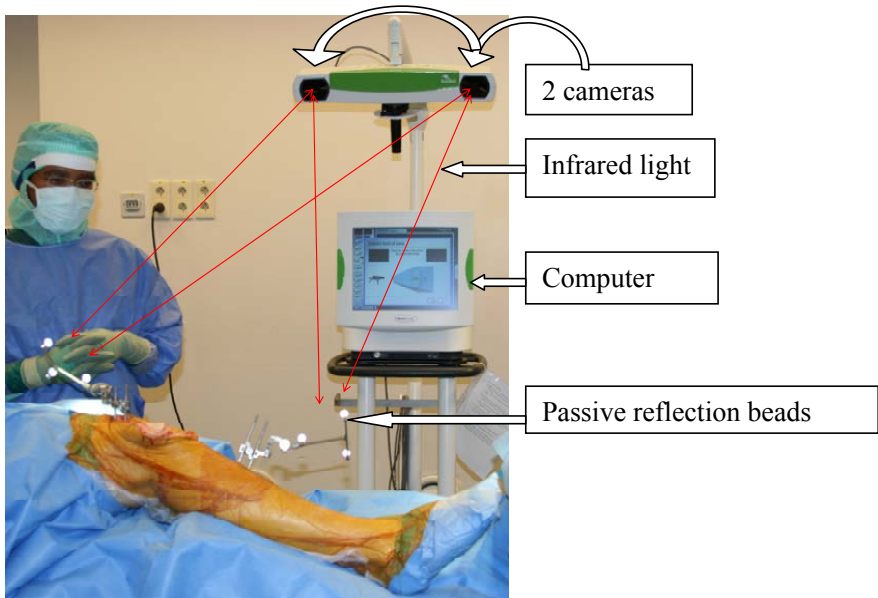


Fig. 1b)

*a) Image on the left showing the limb alignment (Hip-Knee-Ankle angle ( $\chi$ )) 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 ( $\alpha$ ) and tibia ( $\beta$ ) 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 extremities 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 deduced as the vertex of a cone (Fig. 3).

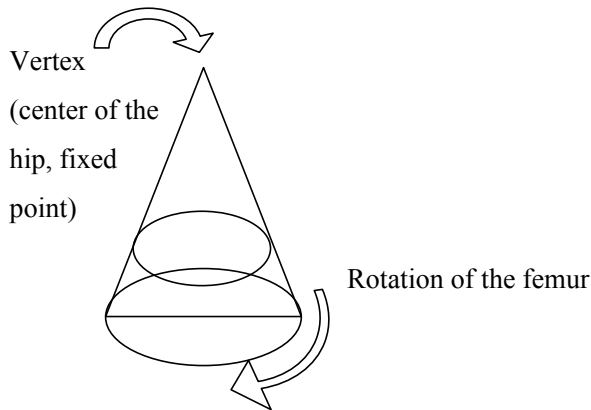


Figure 3. Image illustrating how the computer calculates the center of the hip to obtain the mechanical axis of the femur.

## 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<sup>26</sup>. The method has an accuracy within 1.5 degrees *in vitro*<sup>27</sup>, compared to 1 degree with the classical infrared light based CAS<sup>28;29</sup>. Comparable accuracy has been obtained in a clinical setting<sup>30</sup>.

## 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<sup>31</sup>.

### **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<sup>32</sup>.

### **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<sup>31</sup>.

### **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<sup>33</sup>.

### **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<sup>34</sup>, and the avoidance of fixation pins in the tibia and femur with potential complications like fracture, pin site pain or pin site infection (occurring in 1.3-1.7% of cases)<sup>15;17;18</sup>. 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<sup>35</sup>. 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).



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## 1.3 Implant designs

Knee replacement started with pure molded inlays and plates of metal. Among the pioneers were Campbell in 1940<sup>36</sup>, and the Norwegian born orthopedic surgeon, Smith Petersen in 1942<sup>37</sup>. 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<sup>38-40</sup>. 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<sup>41;42</sup>. 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<sup>43;44</sup>. 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<sup>45</sup>. 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 <sup>46;47</sup>. 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) <sup>48</sup>.

## 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 <sup>49</sup>. 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 <sup>50</sup>. 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

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perpendicular to this axis<sup>51</sup>. 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<sup>52</sup>. 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<sup>53</sup>. 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<sup>54</sup>.

## 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<sup>55</sup>. 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<sup>56;57</sup>.

### *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



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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<sup>58</sup>. 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<sup>59</sup>. The registration of knee replacements started in 1994<sup>60</sup>, 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<sup>61</sup>.

### 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.

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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<sup>62</sup>. 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”<sup>52;63</sup>, 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<sup>64</sup>. 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

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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 3 months 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),<sup>65</sup>.

### **3.4.4 Ethics (RCT)**

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



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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. Prefix 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.

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*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.

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*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<sup>66</sup>. 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,



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many aseptic loosening 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.<sup>67;68</sup>). 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.

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### 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<sup>69</sup>. 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<sup>70</sup>. 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<sup>56;57</sup>. 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

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complications were regarded similar with or without CAS, in this model. We know from our RCT (paper IV) and other trials<sup>71</sup> 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

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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<sup>72</sup>.

### *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



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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<sup>73</sup>. 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<sup>73</sup>.

### *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<sup>74</sup>. 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 adaptations to the Perth protocol)*

The radiological measures were based on the Perth protocol<sup>8</sup>, 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

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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.

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## 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<sup>45;75</sup>. 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<sup>76</sup>. 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*



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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 <sup>77</sup>. 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

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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 <sup>78</sup>. 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 <sup>79</sup>. 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 <sup>14</sup>, 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 Prefix 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

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compensate for this difference<sup>80</sup>. 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<sup>81;82</sup>, and it does not seem like CAS is the solution to this problem<sup>22</sup>. 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.

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### 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<sup>83</sup>. 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<sup>84,85</sup>.

### *Is alignment the target?*

Several authors have reported improved alignment with CAS<sup>86-89</sup>, and a recent meta-analysis of randomized controlled trials concluded that CAS does improve mechanical leg axis and component orientation in total knee replacement<sup>90</sup>. It remains controversial however, whether the improvement of alignment resulting from CAS gives better function<sup>21,91,92</sup> or longevity<sup>93</sup>. 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<sup>94</sup>. These assumptions have been questioned by others, and other values have been suggested<sup>95</sup>. 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<sup>96</sup>. 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<sup>97</sup>. 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<sup>98,99</sup>. Choong et al reported that good alignment correlated with good function<sup>100</sup>. They suggested this correlation was due to the use



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of CAS, in concordance with the dominating belief that alignment is important for good clinical results and longevity<sup>101-103</sup>. 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<sup>21;87;92;104;105</sup>. A CT scan comprises the possibility of detecting both malrotation and malalignment, which might affect clinical function<sup>106</sup>.

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<sup>23</sup>. 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<sup>24,83</sup>. 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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