Efficacy, effectiveness and efficiency of perioperative care and rehabilitation intervention after hip and knee arthroplasty

PhD thesis

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Preface

This thesis is based on studies conducted during my employment as researcher in The Orthopaedic Research Unit, Regional Hospital Holstebro in the period 2004-2007. The studies are carried out in the orthopaedic clinic at Regional Hospital Holstebro.

I am deeply indebted to a number of persons who have made this work possible.

First of all I would like to thank all the patients who have participated in my studies.

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I am especially grateful to my two mentors and friends Charlotte Leboeuf-Yde and Torben Bæk Hansen for their believing in me, for teaching me, and for fruitful discussions.

Finally, I want to thank my family, my wife Hanne Larsen and my children Rasmus and Nanna Nikoline for their ever lasting love and support.

Kristian Larsen
Holstebro, February 2008

List of publications

This thesis is based on a systematic and critical review of the literature and the following papers:

I. Larsen K, Sørensen OG, Hansen TB, Thomsen PB, Søballe K. Accelerated perioperative care and rehabilitation intervention for hip and knee replacement is effective! Acta Orthopaedica. Accepted for publication.

II. Larsen K, Hvass KE, Hansen TB, Thomsen PB, Søballe K. Effectiveness of accelerated perioperative care and rehabilitation intervention compared to current intervention after hip and knee arthroplasy. Submitted.

III. Larsen K, Hansen TB, Thomsen PB, Christiansen T, Søballe K. Efficiency of accelerated perioperative care and rehabilitation intervention after hip and knee arthroplasty. Submitted.

Some additional data, not previously published have been included in the thesis.

Abbreviations

DHAR	Danish Hip Arthroplasty Register
DKAR	Danish Knee Arthroplasty Register
DRG	Diagnosis-Related Group
GLM	Generalized linear models
HRQOL	Health related quality of life
HHS	Harris Hip Score
HTA	Health Technology Assessment
KSCRS	Knee Society Clinical Rating System
LOS	Length of stay
LPR	"Landspatientregisteret" [in Danish]
LPRE	"Landspatientregisteret" [in Danish] enriched with DRG data
NNT	Number Needed to Treat
OLS	Ordinary least square regression
QALY	Quality-adjusted life-year
RCT	Randomized clinical trial
SD	Standard deviation
SHAR	Swedish Hip Arthroplasty Register
SKAR	Swedish Knee Arthroplasty Register
SKS	"Sygehus klassifikations system" [in Danish]
THA	Total hip arthroplasty
TKA	Total knee arthroplasty
UKA	Unicompartmental knee arthroplasty
USA	United States of America

Contents

1. English summary

BACKGROUND In Denmark approximately 10,000 elective primary hip and knee arthroplasties were performed in 2004, and the hospital costs were close to US$ 100,000,000. Accelerated perioperative care and rehabilitation interventions are currently implemented, although the evidence is weak. No evidence of efficiency in a societal perspective exists. Few studies have described the implementation process or how results obtained in effectiveness studies corresponds to results obtained in efficacy studies. We therefore investigated the efficacy and efficiency of perioperative care and rehabilitation intervention compared to the current intervention after hip and knee arthroplasty. If efficacy and efficiency could be demonstrated, we then aimed to describe the implementation process and to investigate if also effectiveness could be demonstrated. We finally wanted to investigate how results from efficacy and effectiveness studies corresponded.

MATERIALS & METHODS Efficacy was investigated in a randomized clinical intervention trial, and efficiency in a piggy-back study to that. We randomized 87 hip and knee patients to either a group receiving the current intervention or a group receiving the new accelerated perioperative care and rehabilitation intervention. In the efficacy study primary outcome was difference in length of stay at discharge. In the efficiency study primary outcome was incremental cost efficacy ratio in a societal perspective, during the first year postoperatively. In the effectiveness study we prospectively documented the implementation process of the accelerated perioperative care and rehabilitation intervention using the Breakthrough Series and active research. We evaluated effectiveness of the accelerated care and rehabilitation intervention in a before-after design including 258 hip and knee patients. Primary outcome was difference in length of stay at discharge.

RESULTS In the efficacy study length of stay was significantly reduced from 8 days in the group receiving the current intervention to 5 days in the group receiving the accelerated perioperative care and rehabilitation intervention. Efficiency was also demonstrated with the accelerated intervention being both less costly and more effective than the current intervention for the hip patients, and being less costly and with equal effect for the knee patients. We documented the Breakthrough Series and active research to function as implementation methods in orthopedics. Length of stay was halved from one year to another after implementation of the accelerated perioperative care and rehabilitation intervention. Length of stay was significantly shorter in the effectiveness study compared to the efficacy study.

CONCLUSIONS An accelerated perioperative care and rehabilitation intervention after hip and knee arthroplasty reach efficacy, effectiveness and efficiency compared to the current intervention. An accelerated intervention can successfully and effectively be implemented within a year. Results obtained in an effectiveness study could actually match result obtained in an efficacy study.

2. Danish summary

3. Introduction

Total hip and knee arthroplasty (THA, TKA) are surgical procedures that involve removal of diseased cartilage and bone, and replacing them with artificial joints (Figure (Fig.) 1-3). They are common, and have become treatments of choice for people with intractable joint pain and disability due to chronic arthropathy who fail conservative management (1). Hip and knee disorders requiring surgery are not restricted to older age group, but may occur at any age (1).

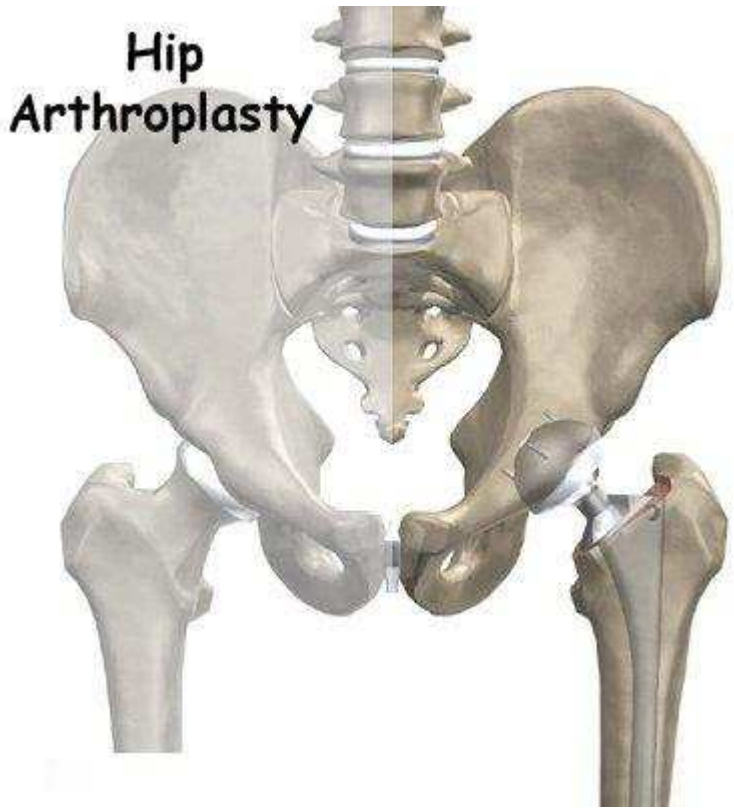

Fig. 1. Total hip arthroplasty

The history of THA started in 1925 by Marius Smith-Peterson from Boston, Massachusetts, United States of America (USA), who moulded glass to be fitted over the ball of the patients' hip joints (2). In 1961, Charnley was the first to demonstrate long-term success by using a prosthetic implant attached to bone with self-curing acrylic cement (1). Current concept in Denmark in 2004 is one third of THA using both uncemented cup and uncemented stem, one third using uncemented cup and

cemented stem, and one third with both cemented cup and stem (operational procedure codes KNFB20, KNFB30, and KNFB40 respectively) (3;4).

The development in TKA lagged behind THA, and earliest attempts failed because of the high stresses on the joint (1). Current concept for TKA is now arthroplasty, in which the femur, tibia, and often the patella are replaced with metal or plastic (Fig. 2) (1). In Denmark 90% of arthroplasties are performed as total arthroplasties, and 6% are medial unicompartmental (UKA) (Fig. 3) (5).

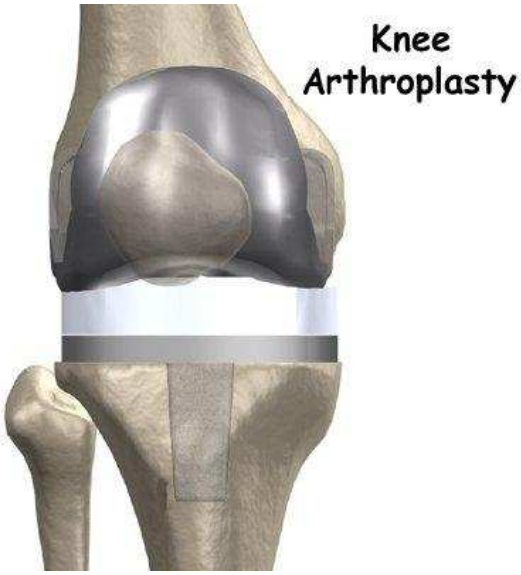

Fig. 2. Total knee arthroplasty

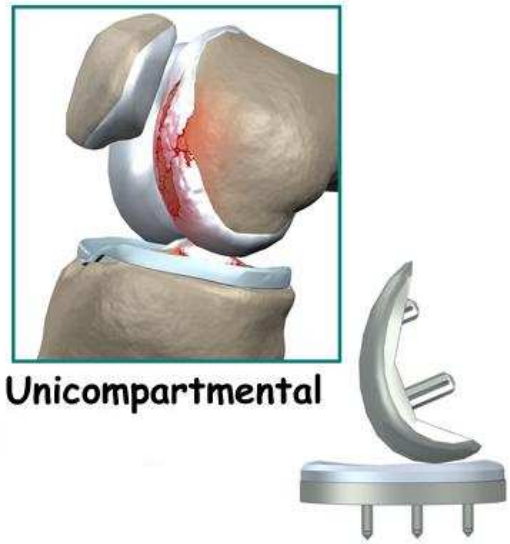

Fig. 3. Unicompartmental knee arthroplasty

UKA is indicated for patients with pronounced medial osteoarthrosis only and normal condition in lateral joint chamber, intact anterior cruciate ligament, and no more than 10° of flexion contracture (operational procedure code KNGB11) (Fig. 3) (4-6). During more than a decade a debate has been going on in the literature if to use UKA, when to use UKA and what is the right proportion of UKA (7). According to the randomized clinical trial (RCT) by Newman *et al*, 1998 they conclude that UKA gives better results than TKA and that the superiority is maintained for at least five years (8). Moreover a cost analysis by Robertsson *et al*, 1999, using SKAR, has shown that UKA actually is cost effective in Sweden (9). But one often mentioned argument in the debate is that UKA is not the primary choice because of the much higher revision rate (7). There has also been a discussion of which operational indications were the right and if there was a need to centralize the operations in fewer more

specialized units or surgeons (7). At least 25% of patients with osteoarthritis at the knee suffer from isolated medial component disease according to a review article by Ackroyd CE, 2003 (10). A total of 76% of the TKA are using cement for all components, 10% are using uncemented components, and 13% are using a cemented tibia component together with an uncemented femur component (operational procedure codes KNGB40, KNGB20, and KNGB30 respectively) (4-6).

The most common cause for THA and TKA are hip and knee pain (1), and the prevalence of hip or knee pain on most days for one month or longer during the past 12 months in the population of people aged 65 years and older is 41% (11). The prevalence of hip pain is 19%, knee pain is 33%, and 11% reports both hip and knee pain (11). Health related quality of life (HRQOL) is worsened with increasing number of symptomatic hip and knee joints (11). The overall prevalence of current hip pain in the population, using a stringent definition, is 7% in males and 10% in females, and becomes more common with increasing age (12). Another cause for THA is fracture of the femoral neck, femoral head or acetabulum (1).

The most common cause of hip and knee pain is primary osteoarthrosis in older people (1). Other causes of hip pain may occur from congenital or developmental dislocation at the birth, Legg-Calve-Perthes disease during the first decade of life, and slipped femoral capital epihysis during adolescence. All childhood hip disorders can lead to degenerative joint disease later on in life (1). Another cause of hip pain affecting all ages is rheumatoid arthritis (1). Knee pain do most commonly occur from degenerations in the joint following minor or major traumatic injuries (1).

No distinct operational indications for THA exits in Denmark. Proposed operational indications for THA are a combination of symptoms, objective and radiological findings. The symptoms are dominated by rest pain, leading to disability, or threatening loss of working ability. Objective sign is reduced movement in the hip joint. The accompanying radiological findings are reduction of joint space, as a sign of destruction of cartilage (13). The most common diagnosis for THA in 2004 by using these indications was primary osteoarthrosis with 80% (classification codes

DM160-169, in Hospital Classification System (SKS)) (3;4). Likewise no specific indications exist for TKA. Common accepted indications for TKA are joint pain, disability and arthrotic changes observed from radiography in weight bearing (6). The most common diagnosis for TKA in 2004 by using these indications was primary osteoarthrosis with 81% (SKS classification codes DM170-179) (4;5).

In 2004, the reported incidence rates per 100,000 person-year at risk for primary THA in the USA, was 140 , whilst the rates for primary TKA was 75 (14). In Denmark the incidence rates of hip replacement was in 2004 estimated to be 142 per 100,000 person-year at risk (3;15-18), and to be 88 per 100,000 for knee replacement (5;15;18), and both incidences are rising (5;15;16;18;19). In 2004, approximately 6,000 elective primary hip and 4,000 elective primary knee replacements were performed in Denmark (3;5;15). Primary THA and TKA are usually successful with less than 1% failure rate per year (3;5). When revision surgery is needed, this is usually because of prosthetic loosening, lysis and component wear and tear (3;5). In this thesis we solely focus on elective primary arthroplasty in the context of chronic arthropathy. In Denmark the total hospital costs for hip and knee replacements was estimated to be close to US$ 100.000.000, when using the Danish Diagnose Related Group tariffs for 2005, as a cost measure (20).

Receiving THA, TKA, and UKA, however, consist of much more than the operation itself and new procedures to optimize the perioperative period, in this study defined as procedures taking place in the period from the preoperative information day, during hospitalization till discharge, have been given several different names, such as accelerated intervention, joint recovery program, multi-disciplinary intervention, multi-modal intervention, fast-track, and clinical pathway. We will use the term "accelerated intervention", which has grown to be the preferred name for this concept in Denmark. The accelerated intervention is a multi-modal intervention taking place in a multi-disciplinary organization consisting of many different departments and healthcare professions (Fig. 4, 5) (21-23) .

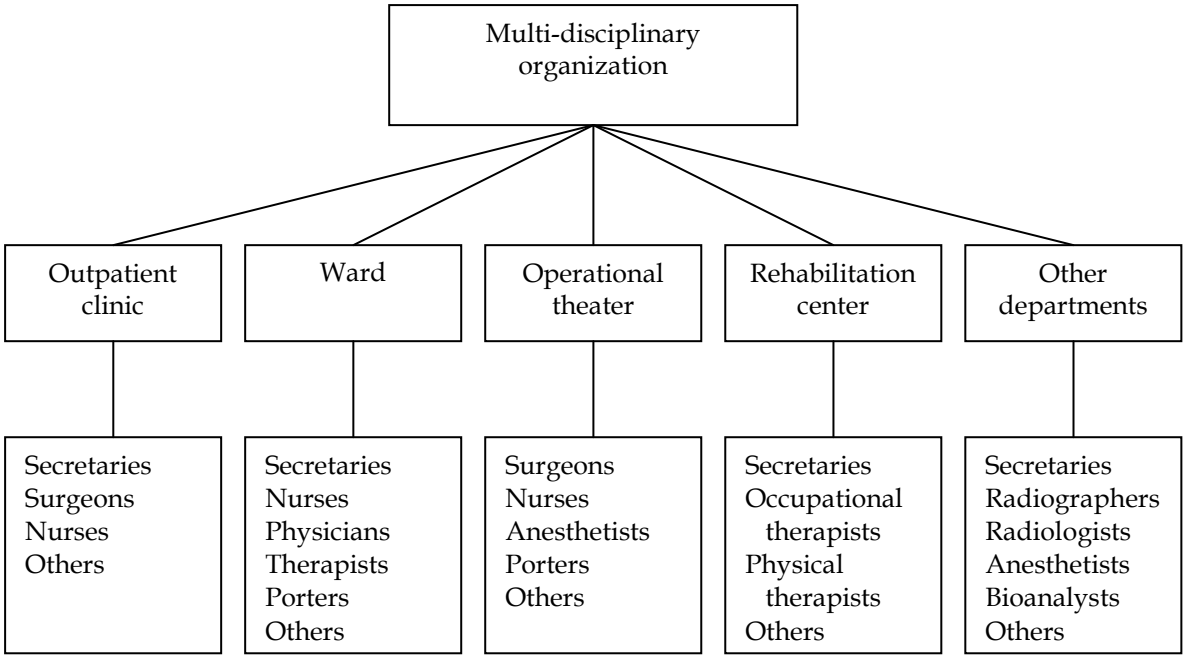

Fig. 4 Departments and professions in a multi-disciplinary organization

The concept of accelerated perioperative recovery program used in this thesis involves a coordinated effort to combine preoperative education of patients, preoperative optimization, attenuation of surgical stress response, optimized pain relief, enforced mobilization, nutritional support, and up-to-date postoperative nursing care and rehabilitation (21-25) (Fig. 8). The concept of accelerated postoperative recovery program has been developed in order to shorten the time needed for convalescence, especially after major surgical procedures, and to reduce perioperative complications (22).

Because an intervention aiming at discharge within 3 days is not the same as an intervention aiming at discharge within 14 days, we will use the following definitions to apply for patients receiving elective primary THA, TKA, and UKA: 1) Super-accelerated intervention is defined as an intervention with planned discharge within 3 days. 2) Accelerated intervention is defined as an intervention with planned discharge within 5 days. 3) Semi-accelerated intervention is defined as an intervention with planned discharge within 7 days. 4) Non-accelerated intervention is defined as an intervention with a planned discharge after 7 days. In historical data, we use these definitions to account for an observed achievement of an average length

of stay (LOS) at or lower than that specified for the relevant group. It is, however, important to understand, that the conditions for discharge must be kept constant (23). In contrast, clinical pathways have been implemented in USA in an effort to reduce LOS and thereby control the hospital costs, whereas less focus has been placed on consequences for patients and society from introducing new accelerated interventions (26).

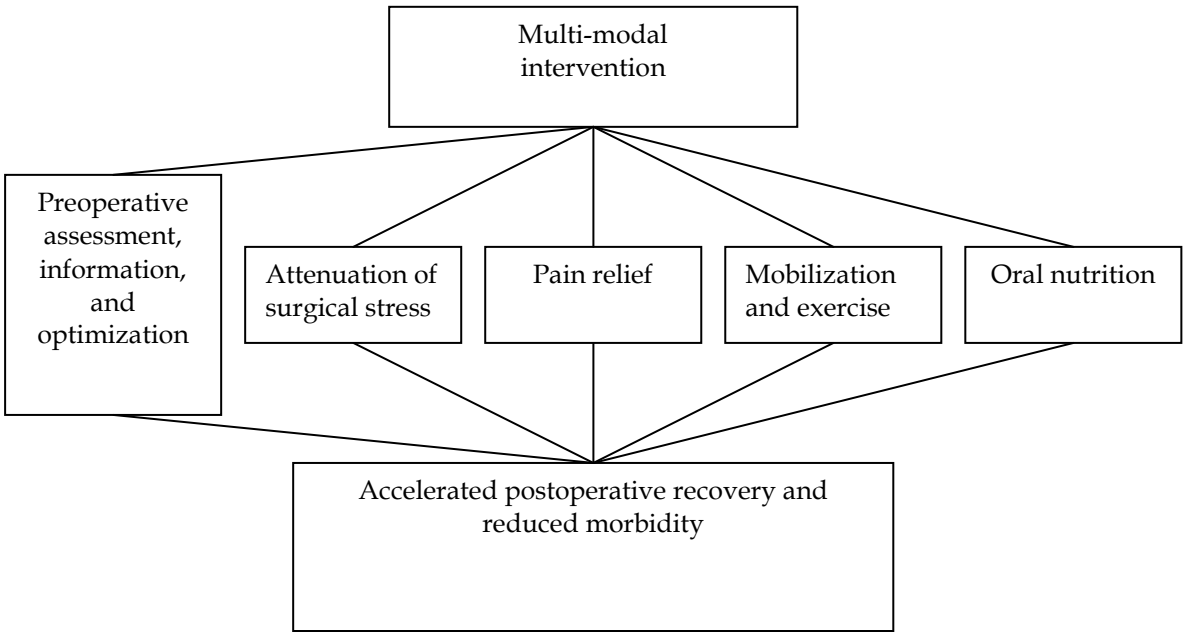

Fig. 5 Multi-modal intervention

Great differences are reported in LOS after THA, TKA, and UKA between hospitals in the USA and Europe (15;19;26). Some of these differences could be explained by different motives for implementation. LOS is, however, a legitimate outcome both in a patient, a hospital and a societal perspective. In the patient perspective prolonged LOS is associated with increased physical decomposition and increased risk of complication (21;23;27-30). In the hospital and societal perspective prolonged LOS is bad administration of limited healthcare resources (31) .

The British pioneer clinical epidemiologist Archie Cochrane defined three concepts related to testing and implementing new healthcare interventions: 1) Efficacy, 2) effectiveness, and 3) efficiency (31;32). 1) Efficacy is the extent to which an intervention does more good than harm under ideal circumstances ("Can it work?").

Ideally, the determination of efficacy is based on the results of a RCT (33). 2) Effectiveness assesses whether an intervention does more good than harm when provided under usual circumstances of healthcare practice ("Does it work in practice?"). Ideally, the determination of effectiveness is established through analyzing the outcome of cohorts of routinely treated individuals, where outcome measurement is already a routine in that environment, and where healthcare staff and patients are not feeling that they are being under study (34). This can be achieved with monitoring studies (routine observations) at a local basis and clinical databases at a central basis, if they use reliable and valid outcomes measures and have a high degree of data completeness. 3) Efficiency measures the effect of an intervention in relation to the resources it consumes ("Is it worth it?") (32). Efficiency trials are more often called cost-effectiveness. In this thesis we subdivide efficiency into two different sub-concepts. A) Cost-efficacy, which studies efficiency at the patient level. B) Cost-effectiveness, which is an efficiency study based on data gathered from more than one source at a population level.

Questions have been raised about the external validity of results in efficacy studies obtained from RCTs programs, especially in cases where representativeness of the study sample could be questioned because of non-participating patients (35;36). Other problems when extrapolating results from efficacy studies to the target population is contamination of the intervention in the control group, and the Hawthorne effect (positive effect of being under study) (33), which potentially can affect both the health care staff and the patients in both the control and intervention groups, and thereby affect the "true result".

Large non-RCT studies can be regarded as some form of transition from efficacy to effectiveness (34). In this thesis we define foreign non-Scandinavian quasi-experimental studies as non-RCT efficacy studies, because they can only bring little information of how an intervention actually does work in a Danish community. Danish and other Scandinavian quasi-experimental studies, however, are regarded as effectiveness studies if they compare cohorts of at least 75 patients, have a routinely use of reliable and valid outcomes, have a high degree of data completeness ($\geq$ 95%),

together with a low degree of awareness from healthcare staff and patients. A least relevant difference in effect of 20% between two interventions can be discovered in two cohorts of 75 patients. To monitor effectiveness of THA, TKA, and UKA clinical databases have been established in many countries of which the Swedish National Hip Arthroplasty Register (SHAR) and the National Swedish Knee Arthroplasy Register (SKAR) are the most known and acknowledges. In Denmark effectiveness data for THA, TKA, and UKA are routinely registered in "Landspatientregisteret" [in Danish] (LPR), and in the Danish Hip Arthroplasty Register (DHAR) and the Danish Knee Arthroplasty Register (DKAR).

Moving from efficacy to effectiveness through implementation of best evidence, however, is a huge problem in health care (37-40), and therefore many different implementation methods have been developed and described (40-42). Overall two implementation approaches are used. A top-down approach where best evidence is collected at a central or national level, and where guidelines are presented for local implementation. The other approach is a bottom-up approach where implementation elements are tested and implemented at a local base, often driven by local resource persons. No evidence exists of which implementation approach is the most effective (40). A potentially effective implementation method for a fast and permanent implementation of new procedures is the Breakthrough Series Collaborative Method, which has been developed by the Institute for Healthcare Improvement (43). The Breakthrough Series has among others been used with success for cardiac surgery in USA (44), but The Breakthrough Series has to our knowledge never been used in orthopedic surgery. Another implementation method that has shown to be effective is to implement new procedures through active research (45). Combing the Breakthrough Series and using research methods during partial and gradual implementation can take advantages from both the top-down and the bottom-up approach.

Musculoskeletal disorders such as chronic hip and knee complaints have a large impact on functional disability, health care costs, sick leave and work disability and have, therefore, substantial economical consequences (46-49). The United Nations,

the World Health Organization (WHO), governments, professional and patients' organisations have therefore declared 2000–2010 the Bone and Joint Decade, with the aim of determining the burden of musculoskeletal diseases and improving the HRQOL of people with musculoskeletal conditions (50;51). Quantifying the health burden of musculoskeletal disorders is critical to decisions involving the allocation of limited health care resources (51). The burden of hip and knee complaints relates not only to its incidence and prevalence, but also to its impact on the HRQOL of the patients who suffer from it (51). When measuring the outcome of THA, TKA, and UKA at the patient level one can use different outcome measures: questionnaires, objective measures of functions, such as gait analysis and strength testing. The questionnaires for THA, TKA, and UKA can be divided into: generic outcome measures such as SF36 (52) and EQ-5D (53) , and disease specific outcome measures such as Harris Hip Score (HHS) (54) and Knee Society Clinical Rating System (KSCRS) (55). Other relevant outcomes are mortality, complications, readmissions, and LOS, most often information of this is taken from registrations in different databases. In this thesis we focus on outcomes from register data regarding mortality, complications, and readmissions because data is considered valid and reliable, and has been through some form of formal validation process (56;57). We also use the generic questionnaire EQ-5D, which measures HRQOL in five dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) (53). EQ-5D has been shown to be both valid and reliable (53;58), and is translated and validated in a Danish population (59). Furthermore Danish Time trades off scores for EQ-5D are established (59). We do not use available data reporting outcome at the patient level from the DHAR or DKAR, as we have found these data to be invalid (results not reported in this thesis).

Evidence of accelerated interventions

Efficacy

Only one review of efficacy of accelerated interventions for THA and TKA could be identified up to 2005 (60). This was a resent review of clinical pathways which included 1 RCT by Dowsey et al. (27) and 10 non-RCT (28-30;61-66). The review

concludes that clinical pathways for THA and TKA reduce LOS and costs (60). In the review three non-RCT (one study reported twice) used accelerated interventions, defined as planned discharge at or within five days postoperatively, and they reported a reduction in LOS ranging from 1.5 to 6.2 days compared to the control intervention (30;65;66). In the study by Scranton, he reported an average LOS of 3.2 days for TKA patients, who were included in a streamlined care path in a orthopedic department in USA in 1995 (66).

The review by Kim et al. 2003, however, was limited to search after articles published in English, in MEDLINE and HealthStar, and used only synonyms for clinical pathway up to 2001 (60). We therefore performed a new search after relevant studies, where we included all randomized clinical trials (RCT) that dealt with accelerated interventions or elements of accelerated interventions defined either as multi-disciplinary organizations or multi-modal interventions, as stated above. Trials were included if the study population were above 18 years of age and had undergone primary elective THA, TKA, or UKA. Primary outcome was LOS, and secondary outcomes were mortality, complications, readmissions, and HRQOL or outcomes from disease specific questionnaires. We sought relevant RCT's in the following databases: the Cochrane Central Register of Controlled Trials, Cochrane Musculoskeletal Group Trials Register, MEDLINE, CINAHL, and EMBASE. All searches were performed up to December 2004. In addition, we searched related articles and reference lists of retrieved articles and references presented in Danish hip and knee guidelines and in Danish year reports from DHAR and DKAR. There were no language restrictions. We searched using both MESH and text words for different combinations of words for THA, TKA, or UKA combined with different words for accelerated interventions. For the full search strategy please refer to Appendix 1. One author extracted data and assessed methodological quality by using the checklist from the CONSORT Statement (67).

Altogether 436 retrieved titles and abstract were screened to se if they contained words for THA, TKA or UKA in combination with words for perioperative accelerated interventions. Only two trials met the inclusion criteria: the trial by Dowsey et al. (27), and the trial by Munin et al. (68), including a total of 261 participants. However, neither of these two studies used interventions which we would define as "true" accelerated intervention.

Qualitative analysis of the two studies showed that the study by Dowsey et al. (27) fulfilled 19 of the 22 criteria in the CONSORT Statement 2001 - Checklist (67), and the study by Munin et al. (68) fulfilled 21 of the 22 criteria.

Pooling of data was not possible due to differences in study design and outcomes. Introduction of clinical pathways and early commencement of rehabilitation led in the two trials to shorter hospital stay, fewer post-operative complications and reduced costs (27;68).

We conclude, that we were not able to identify any evidence of efficacy of accelerated intervention, defined as planned discharge at or within five days postoperatively, compared to current interventions. There was, however, some positive but weak evidence that clinical pathways may be effective, and that it is seams beneficial to mobilize earlier compared to later.

Effectiveness

Effectiveness of current and accelerated interventions was obtained through contact to the Danish National Board of Health and Danish Orthopaedic Society, where we identified relevant Danish registers and Danish and Scandinavian clinical databases and reports. We included data for patients if they in year 2002-2004 received elective primary THA, TKA, or UKA (procedure codes KNFB20, KNFB30, KNFB40, KNGB11, KNGB20, KNGB30, and KNGB40). This was combined with a literature search which was performed using the same search strategy as described above, and in Appendix

1, except from a restriction to randomized clinical trials or clinical trials performed on Danish patients. Primary outcome was to identify number of Danish clinics using accelerated intervention defined as an observed average LOS of $\leq$ 5 days, and to describe average LOS in all Danish public hospitals including clinic Holstebro. LOS was defined as days in hospital (i.e. including days after referral to other wards). Secondary outcome was if possible to describe differences in mortality, readmissions, HRQOL, and disease specific outcomes between accelerated and non-accelerated clinics.

We identified LPR, which we considered the most relevant overall register. We did, however, use the enriched register extended from this on E-Sundhed [in Danish] (LPRE), which is available from a closed database on the Internet. Information at patient level consists among other of gender, age, diagnosis codes, procedure codes, LOS, complication codes, and readmissions. We identified two Danish clinical databases for THA and TKA/UKA: DHAR with latest report in 2004 (3) and DKAR with latest report in 2004 (5). Furthermore four Scandinavian clinical registers for THA and TKA with latest report in 2004 were identified: SHAR, SKAR, The Finnish Endoprosthesis Register, and The Norwegian Arthroplasty Register (7;69-71).

A total of 9,969 elective primary THA, TKA, and UKA patients were identified in LPRE. Of these 9,894 patients (99%) were treated in public hospitals. We did not find any Danish clinics fulfilling our definition of accelerated intervention. However, two clinics using semi-accelerated interventions in 2004 were identified: orthopaedic clinic at Hvidovre Hospital, which has been the leading clinic in Denmark in implementing accelerated interventions, and orthopaedic clinic at Randers Hospitals. Average LOS was 5.2 (standard deviation (SD), 7.1) days in orthopaedic clinic Hvidovre, and 6.7 (SD, 2.8) days in orthopaedic clinic Randers. Average LOS in all Danish public hospitals was in 2004 9.2 (SD, 7.0) days. Average LOS in orthopaedic clinic Holstebro was 9.4 (SD, 3.9). No data on LOS was reported in any of the reports from the Scandinavian clinical registers for THA, TKA, and UKA.

No Danish data of HRQOL was identified. Data was, however, obtained for HRQOL for THA in Sweden. In 2002, SHAR started to register pre- and postoperative HRQOL using EQ-5D, prior to that a pilot testing in different regions has been performed since 1996 (71). In 2004, the average postoperative HRQOL at 6-years follow-up, for a cohort of 1,791 patients with a 95% response rate, was 0.73, which was almost identical to an age-matched population (71). We assumed that HRQOL reported from Sweden represents HRQOL for the current non-accelerated interventions. No effectiveness data on HRQOL for TKA or UKA was identified. In DHAR and DKAR they use disease specific outcome measures (HHS, KSCRS). However, the follow-up rate for these were only 67% in DHAR, and 48% in DKAR, which means that they of little or no use in determining effectiveness of interventions (5;72).

Besides the identified registers, eight Danish non-RCT studies, of which only two was relevant, were identified (73;74). The Danish study by Rasmussen et al. (74), however, was performed in a private hospital, in which results probably can not be generalized to public hospitals, and in the other Danish study by Husted et al. (73) they did not use accelerated interventions as defined above by us.

We conclude that no evidence of effectiveness of accelerated versus current interventions could be identified, however, clinics known to use semi-accelerated interventions had a LOS that was much lower than the observed average LOS for THA, TKA, and UKA in Denmark.

Efficiency

Our search for efficiency studies of accelerated intervention for THA, TKA, and UKA followed the above described search strategy. The search retrieved 76 studies, of which 12 were reviews. The retrieved studies were screened in titles and abstract to se if they contained words for efficiency study, accelerated interventions, and THA, TKA, and UKA.

We were only able to identify one study, the study by Scranton (66). He demonstrated a cost saving of US$ 1,063 for TKA patients who followed a streamlined care path. His study, however, was not an efficiency study in a societal perspective. It is therefore not known how the intervention affects other healthcare sectors. We were not able to find any evidence from efficacy studies of the consequences of accelerated procedures outside the hospital.

Summary of evidence

In summary, THA, TKA, and UKA are common and costly procedures, and research in accelerated perioperative care and rehabilitation interventions after THA, TKA, and UKA is relevant. There is insufficient evidence of efficacy, effectiveness, and efficiency of accelerated interventions compared to the current intervention after THA, TKA, and UKA. There is, however, promising results from accelerated and semi-accelerated Danish and foreign studies.

4. Aim of the thesis

The overall aim of this thesis was to investigate if accelerated perioperative care and rehabilitation intervention after hip and knee arthroplasty could demonstrate efficacy compared to current intervention, in a hospital and patient perspective, and if so, if it could further demonstrate efficiency in a societal perspective. Finally if given efficiency in a societal perspective could effectiveness actually then be demonstrated?

The specific aims were:

I. To investigate the efficacy of accelerated perioperative care and rehabilitation intervention compared to current intervention, after THA, TKA, and UKA, in a hospital and patient perspective.

II. To investigate the cost-efficacy of accelerated perioperative care and rehabilitation intervention compared to current intervention after THA, TKA, and UKA, in a societal perspective.

III. To investigate the effectiveness of an accelerated perioperative care and rehabilitation intervention compared to current intervention after THA, TKA, and UKA, in a hospital and patient perspective.

IV. To investigate if effectiveness results for LOS could match efficacy results for LOS.

5. Materials & methods

A comprehensive description of methodology is referred to the respective publications, which are attached as Appendix 2, 3, and 4.

Ethical issues

The study protocol including all trials was approved by the Medical Ethical Committee of Ringkjobing and Southern Jutland Counties (Ref.: 2627-04). The procedures followed in the studies were in accordance with the ethical standards of the responsible committee on human experimentation and with the Helsinki Declaration of 1975, as revised in 2000. The studies was furthermore registered in The Danish Data Protection Agency (J. no. 2004-41-4753), and the Clinical Trial Register (NCT00175201).

Design

Overall design

The overall design was a health service research design, defined as a scientific study of the tasks, resources, activities and results of clinical practice (75) (Fig 6).

Specific designs

We used a RCT to answer aim I (efficacy study) in cohort B (Fig. 6). In the RCT we followed the recommendations by the CONSORT Statement (67). We used a piggy-back study (economic study alongside a randomized clinical intervention trial) to the RCT for aim II (efficiency study), in an extended follow-up of cohort B (Fig. 6). We used a before-after design for aim III (effectiveness study) with cohort A in the before period and cohort C in the after implementation period (Fig. 6). In this clinical intervention trial we likewise followed the recommendations of the CONSORT Statement (67). The before-after study was part of a monitoring study started in 2003, which routinely monitors outcome for all THA, TKA, and UKA patients operated in

the orthopedic clinics at the Regional Hospital Holstebro and the Regional Hospital Herning. The RCT was nested in the before-after trial, where the intervention group in the RCT was part of the implementation process.

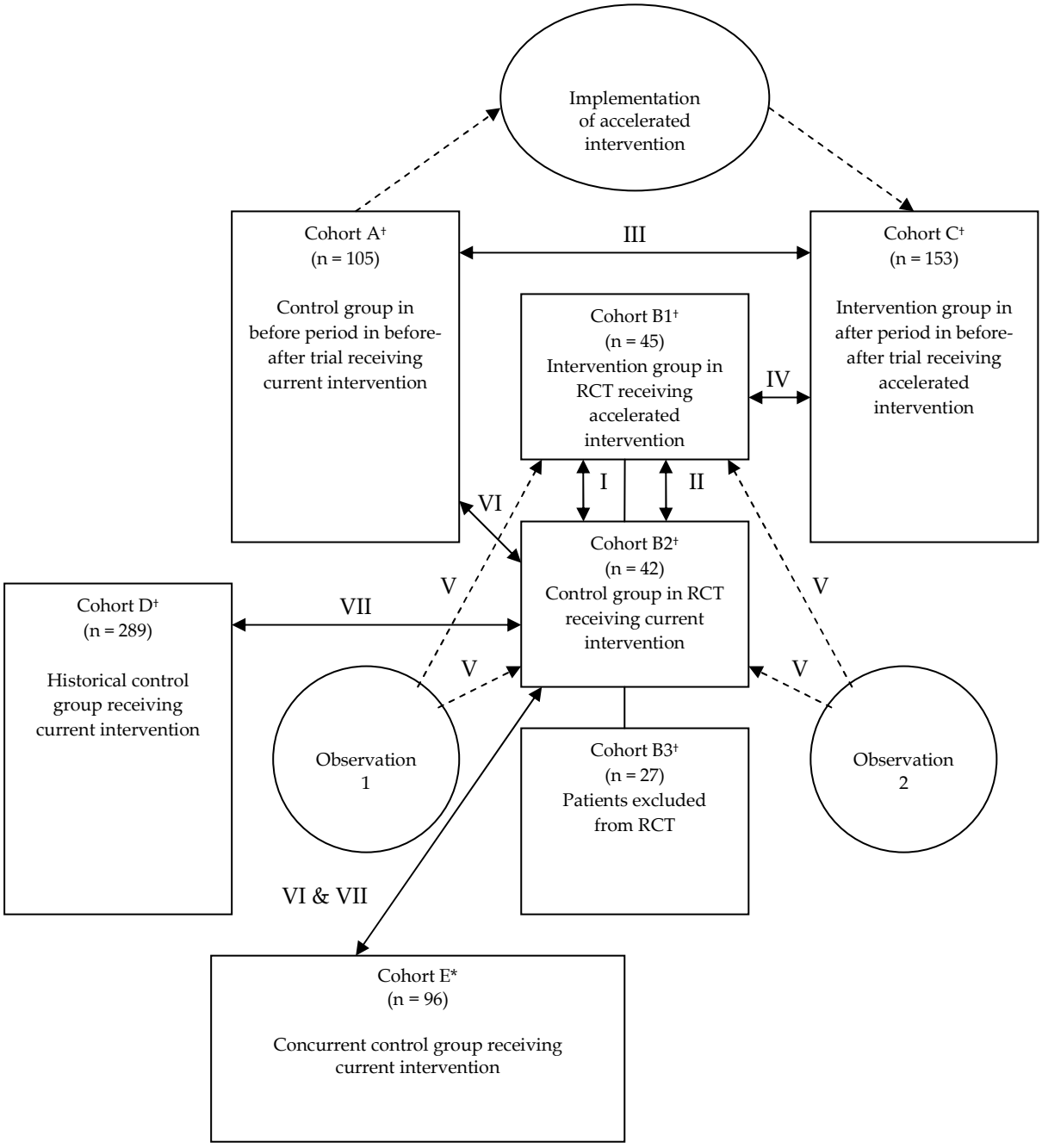

Fig. 6. Overview over the five cohorts (A-E) with a total of 757 patients used to investigate the four aims (I-IV): I) efficacy, II) efficiency, III) effectiveness, IV) efficacy compared to effectiveness, and V) supplementary analyses of a potential contamination effect in the control group, and a potential Hawthorne effect in control and intervention groups, for patients receiving THA, TKA, and UKA at the Regional Hospitals Herning and Holstebro† 2004-2006*

Patients

Altogether 757 patients in five cohorts (A-E) receiving elective primary THA, TKA, and UKA in the Regional Holspitals in Holstebro and Herning from 2004 to 2007 were included (Fig. 6).

Efficacy and efficiency study

All patients, who were planned to undergo elective primary THA, TKA, and UKA in the orthopedic clinic at the Regional Hospital Holstebro, were consecutively invited to participate in the study (cohort B). The exclusion criteria were patients who were 1) mentally disabled or 2) had severe neurological diseases. The estimated sample size at follow-up was calculated using actual data on LOS from the Regional Hospital Holstebro in 2004 together with the results from a pilot study in the first half of 2005. The risk of performing a type-1 error was set at 5% using a two-sided analysis, and the power of detecting a true difference was set at 80%. LOS was expected to be 8 days (SD 4.0) in the control group, and 6 days (SD 2.0) in the intervention group. Using a two-sample comparison of means, we needed at least 40 patients in each group, at follow-up. To account for a potential loss of patients, 90 patients were included. The study took place from August, 2005 to May, 2006. All patients who met the inclusion criteria were given written and oral information of the study at the initial visit, and those who were interested patients gave their written consent. The patients were randomized to either the current procedure group (control group) or the new accelerated procedure group (intervention group) (Fig. 6). After randomization, the patients filled in a baseline questionnaire

Effectiveness study

All patients receiving primary elective THA, TKA, or UKA at the Regional Hospital Holstebro in the pre- and postimplementation periods were consecutively included in the study. Patients receiving acute and revision surgery were excluded. Sample size was calculated from an alpha set at 0.05, a beta set at 0.95, average LOS estimated to be 8.0 days (SD 3.0) in the preimplementation period, and least relevant difference set at 1.5 days. At least 104 patients were therefore needed in both groups. For practical reasons, we decided that the two study periods would be of equal

length, and we therefore included patients in the preimplementation period if they were operated on between January and April 2005 (cohort A) and in the postimplementation period if they were operated on between September and December 2006 (cohort C), at the Orthopedic Clinic at Regional Hospital Holstebro (Fig. 6).

Efficacy compared to effectiveness

We used cohort B1 and cohort C, which received the same accelerated intervention, however, was performed in two distinctive multi-disciplinary organizations, in order to describe how efficacy results in a best case scenario compared to effectiveness results in a real case scenario (aim IV) (Fig. 6).

Intervention

The current procedure for THA and TKA was observed, and analyzed during a 6-months period, from June 2004 to December 2004, and further followed in the preimplementation period. A detailed description of these procedures was made (not presented in this thesis). We then developed a new accelerated intervention from the results of the description and evaluation of the current procedure together with the results from the literature search, and the description of the regimes from the Unit of Perioperative Nursing Care, Rigshospitalet, Denmark (76). A new special care and rehabilitation unit with four male and four female beds was established, whereby the patients were treated in groups and the health care staff concentrated on controlling the postoperative patho-physiology and rehabilitation. All staff allocated to the new perioperative unit received education and participated in a pre-study learning session from January 2005 to May 2005. After evaluation of a pilot study in 23 patients during May and June 2005 the final accelerated intervention was defined in detail.

Control and intervention group

Patients in both groups were having identical operational procedures, defined as all procedures in the timeframe from leaving the ward for operation till they were back in the ward after operation. Operational procedures were following Danish

guidelines (6;13). The attenuation of surgical stress response in both groups was thereby identical. Medication for pain relief was likewise identical in the two groups, and there was no intentional difference in pain relief in the two groups. The areas to investigate in the accelerated intervention were therefore the remaining elements from the multi-modal intervention: preoperative assessment and information, oral nutrition, early and aggressive mobilization and exercise and the multi-disciplinary organization, which we hereafter define as accelerated perioperative care and rehabilitation intervention.

Control group

Patients were hospitalized on the day before surgery, and placed in a general orthopedic ward. They were given hospital clothes to be worn during the whole stay. During the day before surgery the patients were individually informed of the procedures by the surgeon, anesthetist, and nurse. Final blood tests, ECG, and radiographs were taken. Immediately after surgery the patient's pain was evaluated, and analgesics were given accordingly. On the day after surgery the patients started training in bed before lunch, and were mobilized out of bed after lunch (Fig. 7). After lunch the patients were mobilized for the first time by a physiotherapist. During the following days mobilization time and exercise volume was increased, in order to reach the discharge criteria. During the stay care was given in response to the patient's actual needs, and rehabilitation was adjusted according to the patient's immediate state.

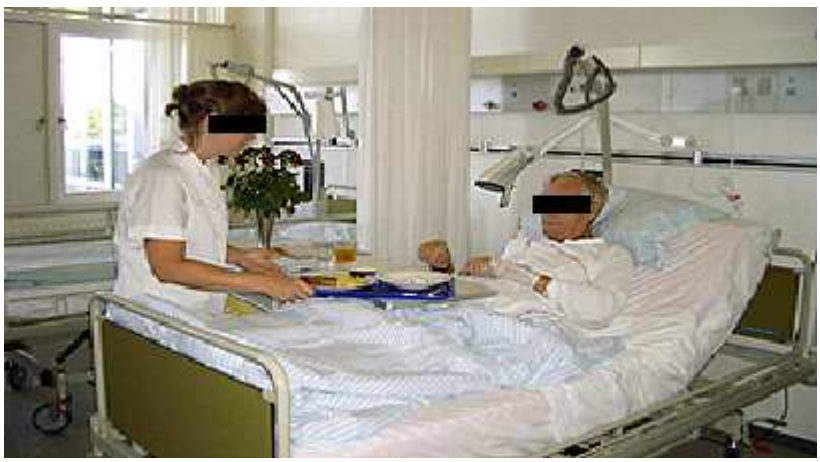

Fig. 7. First day postoperatively for at patients in the current intervention group

Intervention group

All patients, accompanied by one relative, were invited to an information and preparation day the week before surgery. The purpose of the information day was both to inform patients about the accelerated course of treatment, and to prepare patients for surgery by individual consultation with surgeon, anesthetist, and nurse. Final blood tests, ECG, and radiographs were taken. The occupational therapist and the physical therapist delivered helping aids, taught and practiced the exercises, which were going to be performed during and after stay, taught and practiced techniques of how to rise from lying and sitting, how to walk with crutches and if necessary, how to walk on stairs. The patients were encouraged to perform exercises and practice walking with crutches until admission.

On the day of surgery, all patients were hospitalized in the new accelerated care unit. The patients wore their own clothes during the whole stay. The health care staff worked to achieve written preset daily goals regarding: 1) information, 2) pain relief, 3) nausea control, 4) nutrition, 5) mobilization, and 6) elimination. 1) Information on the information day focused on partial goals during the hospital stay, a planned discharge on the fourth postoperative day, how to relieve pain, mobilization strategies, and delivering of means of aid. 2) Pain relief consisted of Oxycontin® / Oxynorm® and paracetamol. 3) Zofran® was used for nausea reduction. 4) A nutrition screening was performed on the information day, and patients were given food according to the result in combination with a daily intake of two protein beverages and a total fluid consumption of at least 2 liters. 5) Mobilization started on the day of surgery. The first postoperative day, the goal was 4 hours out of bed, including training with physiotherapist and occupational therapist (Fig. 8).

We tried to achieve more than 8 hours of mobilization per day for the rest of the hospital stay. Mobilization consisted of all activities out of bed, gait training and exercises. The physiotherapist was responsible for coaching the patient during exercises and gait training. Exercises were focusing on strengthening hip and knee muscles and how to avoid restricted movements. The exercises did not differ between the two intervention groups; however, there was much more focus on

intensity, number of repetitions and progression in the accelerated intervention group. The patients were taught how to increase exercise and gait training after discharge. The occupational therapist was responsible for instruction in how to perform personal needs for the THA patients. All professions were aware of using all situations for functional training, but also that the patients got needed rest time. 6) For elimination we used Magnesia®. Patients likewise followed a diary with the above mentioned preset goals for nutrition, fluid consumption, and mobilization.

Fig. 8. First day postoperatively a patient team in the accelerated intervention group

For further detailed information regarding the accelerated intervention, please see The Unit of Perioperative Nursing Care (homepage on the Internet) (76).

During the study period, a preplanned new procedure for the TKA patients was introduced in 2005, whereby patients fulfilling the criteria for UKA were offered this arthroplasty.

Discharge criteria

Discharge criteria were kept unchanged during the entire study period, except from a criterion for knee flexion, which was omitted in the postimplementation period. Both a physician, not else participating in the study, and the patients had to agree that all criteria were fulfilled before discharge. The criteria were: 1) acceptance of discharge, 2) sufficient pain control, 3) aware of procedures for ending medication, 4) knowing the restrictions, 5) being able to correctly rice from lying and sitting 6) being able to walk safely with or without walking aids, 7) if necessary, being able to walk on stairs, 8) being able to perform home exercises, 9) knowing how to increase home

exercises, 10) being able to perform personal needs, 11) helping aids delivered and installed, and 12) surgical wound showing no signs of infection 13) in knee patients, at least 90^{o} of knee flexion .

Methodological consideration

Attempts to reduce bias in efficacy and efficiency studies

Randomization in RCT

The purpose of randomization in a trial comparing two groups is to ensure that the groups differ only with respect to the interventions being compared (77). A secretary not otherwise involved in the study performed a stratified randomization by drawing an opaque envelope with a number from one of three boxes. The identities of 58 THA patients were drawn from a box with 60 envelopes. The identities of 28 TKA patients were drawn from a box with 30 envelopes, and finally 4 patients going to have UKA were drawn from a box with 4 envelopes. The sizes of the hip and knee patient groups were obtained from the observed ratio in 2004 and 2005 for THA, TKA, and UKA.

Contamination

The two patient groups and their health care staffs were kept separated during the study period, and health care staffs were not allowed to discuss the intervention. Two newly employed therapists, not familiar with the current procedures, were mostly responsible for the rehabilitation in the intervention group. Healthcare staff in the control group was not aware of the procedures in the intervention group. However, in order to describe occurrence of a potential contamination in the control group in the RCT, we used an observational study in cohort B (analysis V) (Fig 6). Two nurses, who were not otherwise involved in the study, examined the size of a potential contamination effect. They performed a structured observation in five areas, which focused on changes between two visits to the two groups (Fig. 6). The five areas they observed were: information, pain control, nutrition, mobilization, and other care and rehabilitation procedures. Besides these five areas the care burden was

observed. The healthcare staff was not aware of being under study for the five mentioned areas, because they were told that the purpose of the observation was to register and describe a potential change in care burden. The registration of care burden was used in the cost-efficacy analysis.

Masking of patients and healthcare staff

As blinding or masking of patients and healthcare staff in the RCT was not possible we included a descriptive study in order to establish the size of a potential Hawthorne effect. We used cohort B2, cohort A and E, which all received the same current intervention, however, was performed in different organizations. In cohort A and E, neither the healthcare staff nor the patients were aware of the ongoing study, while both patients and healthcare staff in cohort B2 were aware of being under study. If contamination in the control group was not present, we would conclude that differences in results occurring between cohort A / E and B2 would be caused by study awareness (analysis VI) (Fig. 6).

Representativeness

We used retrospective and prospective descriptive studies to analyze representativeness of our study sample in the RCT (cohort B) (Fig 6). We collected data from a historical control group (2004 data from Regional Hospital Holstebro) and a concurrent control group (2005 data from Region Hospital Herning). The hospitals of Herning and Holstebro share a common direction, but covers different geographical part of the Central Denmark Region. We considered the two hospitals to be similar regarding the current intervention procedures in the study period. No significant differences between the two hospitals could be identified regarding sex, age, diagnoses or operational procedures in 2004 and 2005.

Change from time

We investigated a potential time-change effect by collecting data from a historical control group (2004 data from Region Hospital Holstebro). We expected a yearly reduction in LOS of 0.8 days in average between the historical control group and the randomized control group, because of an observed trend on reduced LOS seen from 2001 to 2004 in Denmark (15;19).

Attempts to reduce observer bias

Because LOS was related to both the intervention and the outcome we used doctors, not otherwise involved in the study, to decide in agreement with patients when discharge criteria were fulfilled. We used register data and questionnaires for all data collection.

Attempts to reduce bias in effectiveness study

Masking of patients and health care staff

The health care staffs in the pre- and postimplementation periods were not aware of the ongoing study, and all data were drawn from ongoing monitoring in the local and central hospital registers (15;19). Likewise the patients were not aware of the ongoing study, and all contacts and questionnaires were part of the usual monitoring practice.

Attempts to reduce observer bias

We likewise used doctors, not otherwise involved in the study, to decide in agreement with patients when discharge criteria were fulfilled. We used register data and questionnaires for all data collection.

Representativeness

We investigated representativeness of our study sample by comparing the case mix in our study sample to other patients operated in public Danish Hospitals. We compared data for gender, age, diagnosis codes, procedure codes, and patient groups (THA, TKA, UKA).

Economic evaluation in the efficiency study

The perspective of the analysis was that of the society, and the timeframe was fixed to 1 year per patient. The analysis was a marginal analysis, in which preoperative patient costs, perioperative patient transportation and time costs, surgery activities costs, and postoperative planned hospital follow-up activity costs were assumed to be equally distributed in the two groups through the randomization process. The

cost-efficacy of the accelerated intervention was estimated by relating the incremental cost of the two interventions to the incremental effect in quality-adjusted life-year (QALY) between the two interventions. The resulting incremental cost-efficacy ratio (ICER) represents the cost per QALY gained in a cost-utility analysis (78). If the new intervention was both less costly and more effective, an estimate of the percent dominance was obtained from a bootstrap simulation. The uncertainty of the ICER was also estimated by using bootstrap simulation. A bootstrap simulation is a non-parametric method in which a random sample of the same size as the original sample is drawn several times with replacement from the original data. The results of the bootstrap sampling are presented in a cost-efficacy plane. The cost-efficacy plane is constructed from the crossing of the *X* axis and the *Y* axis. Incremental effect is plotted on the *X* axis and incremental cost on the *Y* axis. The four resulting quadrants represent the potential outcomes in cost and effect. In the upper right quadrant the new intervention is more effective but also more costly than the comparator, in the lower right quadrant it is both more effective and less costly, in the lower left corner it is less effective and less costly, and finally in the upper left quadrant it is both less effective and more costly (79).

Costs

The primary cost estimate was average total costs (cost estimate A). Postoperative productivity loss was calculated according to the friction method with a maximum of 3 months of absenteeism from paid work (80). We obtained all primary sector costs (i.e. medical care, medication, physiotherapy) from referral 12 weeks preoperatively to hospitalization from a regional register (81), in order to adjust the postoperative cost for any preoperative use of a medical doctor, physiotherapy, and medication. We started estimation of costs at the information day, 3 to 4 days before surgery, for the accelerated intervention patients and at the day of admission, the day before surgery, for the current intervention patients. Time ended at the 1-year follow-up at which a questionnaire was used. We estimated the total costs at the patient level using a mix of activity-based-costing analysis, and the step-down method of allocation of overhead department costs to the final department. We defined seven activity centers: 1) information day, 2) hotel management, 3) care, 4) rehabilitation, 5)

follow-up patients, 6) follow-up primary sector, and 7) follow-up hospital) to cover the production path (Fig. 9).

Total average costs in the seven activity centers were calculated and gathered in three cost categories (i.e. pre-, peri- and postoperative costs) by multiplying the observed volumes of health care with the unit prices. 1) Information day activities were identified from observation and time registration, and validated with health care staff. 2) Hotel management costs were calculated from the hospital central accounting system using step-down allocation of overhead department costs to the final department and finally estimating a daily hotel cost. 3) Care activities and 4) rehabilitation activities were identified from observations and time registration, and validated with health care staff. 5) Follow-up patient activities and 6) follow-up primary care were obtained from standardized and validated patient diaries (82) and questionnaires, and were validated against the hospital patient administrative system and Ringkoebing Amts Sygesikringsregister [in Danish] (81). 7) Finally follow-up hospital activities were obtained from the hospital patient administrative system observing any readmissions in the period from discharge to 3 months past discharge.

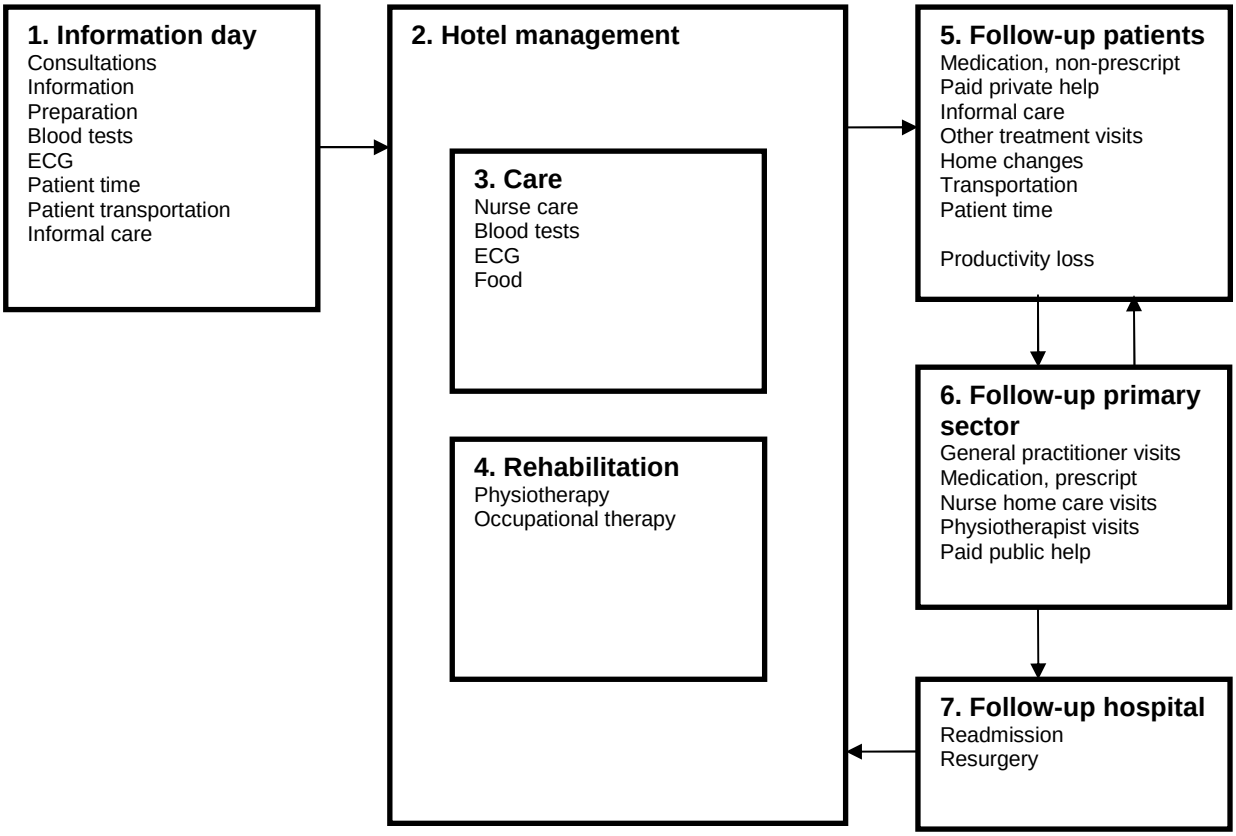

Fig. 9. Pre-, peri-, and postoperative costs in seven activity centres for 87 patients receiving total hip, total knee, and unicompartmental knee replacement, Denmark 2005-2006

Unit costs

Unit costs were obtained from the central Danish hospital employee register (83), Ringkoebing Amts Sygesikringsregister [in Danish] (81), StatBank Denmark (84), The Dutch manual for costing in economic evaluation (85), and from patient reporting. The average number of effective working hours was calculated to 1,516 hours by using actual hospital wage and employee data. Costs in activity centers 1 to 4 were calculated in 2005 prices, and transformed to 2006 prices after adjusting for inflation. Costs in activity centers 5 to 7 were calculated using 2006 prices. Productivity loss for patients engaged in active employment was calculated by using an average wage rate for the age-specific group, while productivity loss for patients not engaged in active employment was calculated by using the proposed tariff in the Dutch Manual for Cost Research (85), after adjusting for inflation. Cost in DKK were transformed to US $ by using the exchange rate of DKK 630.82 for 100 US $, obtained on January 2 2006, from the Internet (86).

Implementation of accelerated intervention

We used the Breakthrough Series Collaborative Model (87), with a preparation, project and spread phases. The spread phase to other wards and hospitals is currently ongoing, but is not reported in this thesis. This implementation method was combined with active research. The implementation process started June 2004 by acknowledging that our current procedure was different from best Danish practice (73;74). Observed LOS in our orthopedic ward for primary elective THA, TKA, and UKA was on average 9.4 days in 2004, which were much longer than LOS reported from other Danish hospitals (73;74). We started our Breakthrough Series with recruiting of a researcher with knowledge of The Breakthrough Series. We then established an implementation organization, enrolled participants, and planned gradual implementation by using three learning sessions, three action periods, and three evaluation periods. Focus in all learning sessions and action periods was to develop an effective multi-disciplinary organization which in a proactive manner could master the multi-modal interventions (21-23;25). The overall aim for the implementation was to achieve a reduction in LOS of $\geq$ 30% compared to LOS in 2004, without increase in mortality or morbidity, and without a shift in burden of care and rehabilitation from secondary to primary sector.

In the preparation phase we established a project leading group in September 2004, which consisted of the clinic head doctor, the clinic head nurse, a new accelerated intervention responsible nurse, and a researcher with knowledge of the Breakthrough Series. A nurse was designated to throughout describe the current perioperative care, and the head physiotherapist was pointed out to describe the current rehabilitation intervention.

The researcher was placed in the orthopedic ward from October 2004 to December 2004. During this period he observed a number of patients from diagnostics preoperatively, during the hospital stay, and at the 3-month follow-up visit. His observations focused on Lean procedures with value stream mapping, and thereby which procedures were true interventions, and which procedures were actually waiting time (88).

From January to March 2005 the new accelerated intervention responsible nurse and the researcher developed and described the new accelerated perioperative care and rehabilitation intervention. The results from their work are in accordance with the procedures describes by the Unit of Perioperative Nursing Care, Rigshospitalet (76).

In March 2005, a multidisciplinary organization group was established with leading personnel from all involved departments (head secretary, clinic head doctor, clinic head nurse, leading ward nurse, head physiotherapist, head anesthetist, head laboratory technician, head of radiotherapy department, and head of the helping aid central) in order to discuss how to implement the new accelerated care and rehabilitation intervention in small scale.

In April 2005 a new special care and rehabilitation unit was established in the orthopedic ward. It consisted of a new multi-disciplinary organization, which was lead by a nurse, and included further eight nurses, one occupational therapist and one physical therapist, and a separate part of the orthopedic ward with 4 male and 4 female beds.

Moving into the project phase we held our first learning session for the new health care staff in the accelerated unit in April 2005 just before the first action period (a pilot study).

During May and June 2005, a total of 23 patients entered the pilot study period: 11 patients were allocated to receive the accelerated intervention, and 12 patients to continue to receive the current intervention. The process and results of this pilot study were evaluated in June 2005.

In August 2005 the multi-disciplinary organization group met, and adjusted the multi-modal interventions for the new accelerated intervention, preparing to introduce the new methods in a medium scale implementation.

In August 2005, our second learning session was held just before the start of our second action period (the RCT period), where 90 patients were allocated to either the current or the accelerated intervention.

Because of significant and positive results obtained in our evaluation of efficacy and cost-efficacy of accelerated intervention compared to the current intervention in action period 2, it was decided in February 2006 to implement the accelerated intervention in full scale to all elective primary THA, TKA, and UKA patients.

After evaluation of the second activity period, the leading nurses who had developed and led the program in the RCT handed over the plans for the multi-disciplinary organization and the multi-modal intervention to new leading personnel, who were put in charge of the last full scale implementation in action period 3. Most of the healthcare staff involved in developing the new accelerated intervention was not part of the new post-implementation staff.

The new multidisciplinary organization group met in February and March 2006, in order to coordinate and adjust according to the results from the second action period, and to plan a full scale implementation.

From March to August 2006, a total of 4-6 patients per week were continuously allocated to the accelerated unit, where they followed the accelerated procedures, including the preoperative information day. All other patients could of logistic reasons not be invited to an information day, but were hospitalized the day before surgery, where as much as possible of the information day information was given. The rest of the stay these patients followed the accelerated perioperative procedures.

In June 2006, we held our third and final learning session for all health care personnel involved with THA, TKA, and UKA patients, just before the full scale implementation. This third action period and post implementation period started in September 2006.

Outcomes

Efficacy in a hospital and patient perspective

Primary outcome was LOS at discharge, and secondary outcome was the patients gain in HRQOL from baseline to 3-month follow-up. LOS was recorded using register information from the hospital registration system. At 3 months after discharge, all patients were seen on an outpatient basis at Region Hospital Holstebro where they filled in a follow-up questionnaire. HRQOL was obtained by using a standardized instrument for measure of health outcome "EQ-5D" (53) at the patient level. HRQOL scores were calculated by using the "Official Danish Time Trade Off scores" (59). Adverse effects were collected from register data on mortality, readmissions, and complications within 3 months postoperatively.

Efficiency in a societal perspective

Primary outcome was ICER defined by

$$ICER = (C_A - C_B) / (E_A - E_B)$$

Where C denotes the arithmetic mean costs and E denote arithmetic mean effects with subscripts of A and B referring to comparators (79).

The follow-up time was extended from 3 to 12 months. Cost and effect data were colleted postoperatively by using a cost diary (82), weekly for the first 12 weeks and questionnaires at 26, 39, and 52 weeks combined with register data. The effect of the accelerated intervention was measured in QALY by using "EQ-5D" (53) to estimate HRQOL. HRQOL scores were calculated by using the "Official Danish Time Trade Off scores" (59), at baseline and weekly from first to 12, 26, 39, and 52 weeks postoperatively. The QALY was then calculated by using the 15 measure points postoperatively to establish the area under the curve (78).

Effectiveness in a hospital and patient perspective

Primary outcome was in hospital LOS from admission to discharge, and secondary outcome measures were adverse effects (readmission within 30 days, and mortality

within 3 months postoperatively). Data on all patients were collected via personal identification numbers from local and central hospital registers.

Statistics

All data were entered twice using EpiData 3.1(89). The data was analyzed using intention-to-treat analysis according to the recommendations in Evidence-Based Medicine (90). All analyses were performed using STATA 9.1, StataCorp, Texas, USA. The significance level was set at $p < 0.05$.

Efficacy in a hospital and patient perspective

We calculated unadjusted crude and stratified THA, TKA, and UKA mean LOS with SD for the intervention group, the control group, and the groups of excluded patients, patients refusing to participate, the concurrent control patients, and the historical control patients. Because of a non-normal distribution of LOS, we calculated the unadjusted crude and unadjusted stratified THA, TKA, and UKA median difference between the accelerated intervention and the current intervention using nonparametric equality-of-median test, combined with Hodges-Lehman median differences with 95% confidence interval.

The adjusted effect of the accelerated intervention on LOS was estimated in a multivariate linear regression analysis, after controlling for assumptions (independence of random deviations, same distribution of random deviations, and normality of random deviations). The analysis included: randomization group, HRQOL at baseline, sex, age as a continuous variable, diagnosis osteoarthrosis or not, cemented implant or not, and the randomization stratification as a covariate. Results are reported for LOS from admission to discharge as well as LOS from day of surgery to discharge. Results for LOS are also presented as proportion being discharged at or before the fifth day, in order to estimate the Number Needed to Treat (NNT) (Sackett et al., 2000).

We calculated unadjusted crude and stratified THA, TKA, and UKA mean HRQOL with SD for the two randomization groups. The unadjusted crude and unadjusted

stratified mean difference in gain, from baseline to follow-up, between groups was analyzed using two-sample t-test. Because of non-normal distributions of HRQOL, unadjusted crude and stratified differences between groups at follow-up were calculated using nonparametric equality-of-median test, combined with Hodges-Lehman median differences with 95% confidence interval.

The adjusted gain in HRQOL from baseline to follow-up was analyzed in a multivariate linear regression analysis, with non-parametric confidence intervals based on 1000 bias-corrected and accelerated bootstrap replicates, according to Manca et al. 2005, after controlling for assumptions. The analysis included: randomization group, HRQOL at baseline, gender, age as a continuous variable, diagnosis osteoarthrosis or not, cemented implant or not, and the randomization stratification as a covariate. Results for HRQOL are furthermore presented as proportion described as "well" at the 3-month follow-up. Well was defined as achievement of a HRQOL at or above the observed age adjusted HRQOL for a Western Danish population (Pedersen KM et al., 2003).

Efficiency in a societal perspective

Univariate analysis of incremental cost and effects were, due to non-normality of data, analyzed by using a non-parametric bootstrap procedure with 2000 bias-corrected bootstrap replicates of the arithmetic mean. Missing values resulting from incompleteness of data were, in accordance with Brunenberg et al. (91), replaced with the mean value of the group. All analyses were performed by using STATA 9.1, StataCorp, Texas, USA. The significance level was tested with the non-parametric percentile method (92).

We also performed multivariate analyses of incremental costs because it can be superior to univariate analysis by explaining variation due to other causes (92). Multivariate analysis of incremental costs (cost estimate A) and effects were estimated by using ordinary least square (OLS) regression with 2000 bias-corrected and accelerated replicates of the incremental difference.

We further performed multivariate analyses of incremental costs with generalized linear models (GLM), because these models seem to be ideal in handling the mean and variance functions on the original scale of skewed cost data (92;93). GLM analysis was performed with log link function and the following families: Gaussian, Poisson, Gamma, and Inverse Gaussion / Wald. Only GLM link function and family are reported that pass all the following tests: Skewness/kurtosis test, Heteroskedasticity test (Breusch-Pagan test), Modified Park test (GLM family test), Pregibon Link test, Modified Hosmer Lemenshow test, Pearson's Correlation test.

In the multivariate analyses, incremental cost was adjusted for any preoperative primary sector cost, HRQOL at baseline, gender, age, diagnosis osteoarthritis or not, cemented implant or not, employed or not, and if hip or knee patient.

Differences between treatment groups were tested by using the non-parametric percentile method (92).

In the multivariate analyses of incremental effect we adjusted in accordance with Manca et al. (94) for HRQOL at baseline together with gender, age, diagnosis osteoarthritis or not, cemented implant or not, and if hip or knee patient.

We finally made analyses with a further three cost estimates (cost estimate B-D) in order to enhance the transferability of costs in different areas within or without the hospital and their consequences for the conclusion.

Cost estimate B was total average costs – average follow-up hospital costs from readmissions, and was estimated because our results could be heavily affected by some fortuitous readmissions in one of the randomization arms.

Cost estimate C was total average costs, average productivity loss, and was estimated because productivity loss is considered a separate cost group (i.e. indirect cost) (85).

For final comparison, a cost estimate D of the total average cost, average follow-up hospital costs, and average productivity loss was made.

Effectiveness in a hospital and patient perspective

The primary analysis was to test the difference in LOS between the current intervention observed in the pre-implementation period and the fully implemented accelerated intervention in the post-implementation period. This analysis represents the effectiveness analysis of the accelerated intervention (aim III). Secondary analysis was to test the difference in LOS reported in the efficacy study with the fully implemented procedures in the post-implementation period, to see whether effectiveness could match efficacy (aim IV). LOS is presented with mean and SD, together with the median and range. Because of a non-normal distribution of LOS, the differences between groups were, tested using the non-parametric percentile method after a multivariate linear regression with 2000 non-parametric bootstrap replicates. The 95% confidence intervals were retrieved from 2000 bias-corrected and accelerated bootstrap replicates. The differences in LOS were adjusted for gender, age, diagnosis, implant type, and patient group (THA, TKA, UKA). Categorical data were analyzed with Fisher's Exact test.

6. Summery of results

Patient characteristics

A total of 117 patients were eligible for the efficacy study. Of these 27 were not included: 23 refused to participate, two were excluded due to mental disability, one patient was excluded because of physical disability from a neurological disease, and one patient was excluded because she did not submit the written consent before surgery. This left 90 patients for randomization. Of these 45 patients were allocated to each group: 30 THA patients to the control group and 28 THA patients to the intervention group. There were allocated 13 TKA patients to the control group and 15 TKA patients to the intervention group. Finally 2 UKA patients were allocated to each group. Three patients in the control group were excluded after randomization (2 THA and 1 TKA). One was excluded because surgery was cancelled due to infection preoperatively, and two because they wanted surgery past the inclusion period. This left 87 patients to receive the allocated intervention: 42 in the control group (28 THA, 12 TKA, and 2 UKA), and 45 in the intervention group (28 THA, 15 TKA, and 2 UKA). Patients in the two groups were comparable at baseline (Table 1). For an overview of other patients please refer to Table 2.

One patient died perioperatively, and LOS for this patient was included from admission to death in the intention-to-treat analysis. Complete data from baseline to 3-months follow-up were obtained from all other patients.

In the efficiency study, we followed all 87 patients who received the allocated intervention for further nine months. Pre- and perioperative cost data were available for all patients. Regarding postoperative cost data, eight patients did not complete the postoperative diary (current intervention: 3 THA and 2 TKA; accelerated intervention: 2 THA and 1 TKA), and 3 patients did not complete any of the postoperative questionnaires (current intervention: 2 THA, and accelerated intervention: 1 THA). Data were, however, obtained for these missing patients from the Ringkoebing Amts Sygesikringsregister [in Danish] (81).

Table 1. Patient characteristics at baseline for 87 patients in randomized clinical trial, Denmark 2005-2006

Group	Accelerated intervention	Current intervention
All (n)	45	42
Female/male ratio	25 / 20	19 / 23
Age, mean (SD)	64 (10.8)	66 (9.2)
Mean HRQOL* (SD)	0.46 (0.28)	0.53 (0.22)
THA† (n)	28	28
Female/male ratio	15 / 13	11 / 17
Age, mean (SD)	62 (11.3)	65 (9.5)
Arthrosis coxae / other	27 / 1	28 / 0
Implant cemented / uncemented ratio	8 / 20	12 / 16
Mean HRQOL (SD)	0.45 (0.30)	0.49 (0.22)
TKA‡ (n)	15	12
Female/male ratio	9 / 6	7 / 5
Age, mean (SD)	68 (9.1)	67 (10.2)
Arthrosis genus / other	15 / 0	11 / 1
Mean HRQOL (SD)	0.44 (0.24)	0.60 (0.22)
UKA§ (n)	2	2
Female/male ratio	1 / 1	1 / 1
Age, mean (SD)	60 (13.4)	61 (6.4)
Arthrosis genus / other	2 / 0	2 / 0
Mean HRQOL (SD)	0.67 (0.05)	0.66 (0.22)

**Quality of life from EQ-5D, † Total hip arthroplasty, ‡ Total knee arthroplasty, §Unicompartmental knee arthroplasty*

Regarding effect data, they were available from all patients at baseline, 3-month, and 12-month follow-up, except from one patient at 12-month follow-up.

In the effectiveness study, a total of 105 patients were included in the pre-implementation period, and 153 patients were included in the post-implementation period. Complete data were available for all 258 patients receiving THA, TKA, and UKA in the orthopedic clinic at the Regional Hospital Holstebro from admission to 3-month follow-up. Patient characteristic are presented in Table 3. No significant differences between the two groups were observed, except for the differences that occur from introduction of UKA in 2005.

Table 2. Patient characteristics at baseline for patients not included in randomized clinical trial, and for patients in a concurrent control, and a historical control group, Denmark 2004-2006

Group	Eligible for randomized study Not included in study		Non-randomized study	
	On criteria	Refused participation	Concurrent	Historical
All (n)	4	23	96	289
Female/male ratio	2/2	14/9	45/51	153/136
Age, mean (SD)	69 (5.5)	67 (10.4)	67 (9.6)	65 (11.6)
THA (n)	3	10	53	179
Female/male ratio	1/2	4/6	35/25	88/91
Age, mean (SD)	71 (5.8)	65 (8.1)	66 (10.0)	64 (12.0)
Diagnosis				
Arthrosis coxae / other	3 / 0	10 / 0	49 / 4	151 / 28
Implant ratio				
Cemented /uncemented	2/1	2/8	26/26	88/89
TKA (n)	1	12	43	110
Female/male ratio	1/0	9/3	20/23	65/45
Age, mean (SD)	65 (----)	70 (11.8)	68 (9.0)	67 (10.56)
Diagnosis				
Arthrosis genus / other	1 / 0	10 / 3	43 / 0	106 / 4
UKA (n)		1		
Female/male ratio		1/0		
Age, mean (SD)		64 (----)		
Diagnosis				
Arthrosis genus / other		1 / 0		

Table 3. Patient characteristic at baseline for 258 patients in the current and accelerated intervention groups

	Current intervention (n = 105)	Accelerated intervention (n = 153)	*P* value
Gender, female vs. male	52 / 53	78 / 75	0.889
Age, mean and standard deviation	65 (11.0)	65 (11.0)	1.000
Diagnosis, arhrosis vs. other	97 / 7	150 / 3	0.095
Implant type, cemented vs. uncemented	37 / 68	41 / 112	0.168
Patient group (THA, TKA, UKA)*	63 / 42 / 0	76 / 66 / 11	0.006†

* *Total hip arthroplasty, total knee arthroplasty, unicompartmental knee arthroplasty*

† *UKA was introduced in 2005 and P value when not splitting knee patients into TKA and UKA was 0.127*

Length of stay

In the efficacy study, mean LOS was 4.9 (SD, 2.4) in the intervention group, and 7.8 (SD, 2.1) in the control group. Overall, there was an unadjusted median reduction in LOS of 3.0 (95% CI 3-4) days in the intervention group compared to the control group ($P < 0.001$). The adjusted mean difference yielded a reduction in LOS of 3.1 (95% CI 2.3-4.0) days ($P < 0.001$). For further information of unadjusted crude, unadjusted stratified and adjusted LOS in the two groups see Table 4. The adjusted mean

difference between the control and intervention group from day of surgery to discharge yielded a reductions in LOS of 1.5 (95% CI 0.7-2.3) days favoring the accelerated intervention ($P < 0.001$).

Table 4. Unadjusted, crude and stratified mean length of stay (LOS) with standard deviations, in the accelerated intervention group and five other groups, receiving the current procedure for 499 patients. Median, and median difference with 95% confidence limits between the accelerated and the current intervention group. Adjusted mean difference in length of stay, Denmark 2004-2006

Group	Eligible for randomized study				Non-randomized patients	
	Included in study		Excluded from study			
	Accelerated intervention	Current intervention	Criteria	Refused	Concurrent	Historical
Unadjusted						
Crude (n)	45	42	4	23	96	289
Mean (SD)	4.9 (2.4)	7.8 (2.1)	8.3 (1.7)	7.2 (1.8)	8.7 (2.8)	9.3 (3.9)
Median	4	7				
Diff.*, CI		3 (3-4)†				
P-value		<0.001‡				
Stratified						
THA, (n)	28	28	3	10	53	179
Mean (SD)	4.4 (1.3)	7.3 (1.5)	9.0 (1.0)	7.6 (1.4)	7.8 (2.8)	9.2 (4.3)
Median	4	7				
Diff., CI		3 (2-4)				
P-value		<0.001				
TKA, (n)	15	12	1	12	43	110
Mean (SD)	6.1 (3.5)	9.3 (2.5)	6.0 (----)	7.2 (1.8)	9.9 (2.5)	9.6 (3.3)
Median	4	8.5				
Diff., CI		4 (2-5)				
P-value		0.035				
UKA, (n)	2	2		1		
Mean (SD)	3.0 (0)	6.0 (1.4)		3.0 (0)		
Median	3	6				
Diff., CI		3 (2-4)				
P-value		0.317				
Adjusted						
Diff., CI		3.1 (2.3-4.0)§				
P-value		<0.001				

** Difference: Median LOS current intervention – median LOS accelerated intervention, † Hodges-Lehman median differences with 95% confidence interval, ‡ Difference between groups tested with Nonparametric equality-of-medians test, § Mean difference with 95% confidence intervals from multivariate linear regression including randomization group, HRQOL at baseline, gender, age, diagnosis, implant type, and randomization stratification*

More patients in the intervention group were discharged at or before the fifth day ($P < 0.001$): 35 of 45 in the intervention group compared to 3 of 42 in the control group (THA 24 vs. 2, TKA 9 vs. 0, and UKA 2 vs. 1). This lead to a NNT of 1 patient (95% CI 1-2) for the new accelerated intervention compared to the current intervention.

In the analysis of effectiveness, we revealed a significant adjusted average reduction in LOS of 4.4 days (95% CI 3.9 – 5.0) from a LOS of 8.8 days (SD 3.0) for all patients receiving the current procedure in the pre-implementation period to 4.3 days (SD 1.8) for all patients receiving the fully implemented accelerated intervention in the post implementation period ($P < 0.001$). Stratified LOS in the post-implementation period for the patients receiving the accelerated intervention was reduced to 4.0 days (SD 1.7) for the THA patients, 4.7 days (SD 1.7) for the TKA patients, and 3.4 (SD 2.1) for the UKA patients. For further information on crude and stratified results for LOS in the current and accelerated groups please refer to Table 5.

Table 5. Length of stay for THA, TKA†, and UKA‡ patients in the two intervention groups*

	Current intervention	Accelerated intervention
Crude (n)	105	153
Mean (SD)	8.8 (3.0)	4.3 (1.8)
Median (Range)	8 (4-21)	4 (2-11)
Stratified		
THA, (n)	63	76
Mean (SD)	8.4 (3.3)	4.0 (1.7)
Median	7 (4-21)	4 (2-11)
TKA, (n)	42	66
Mean (SD)	9.4 (2.4)	4.7 (1.7)
Median	8.5 (6-15)	4 (2-11)
UKA, (n)		11
Mean (SD)		3.4 (2.1)
Median		3 (2-9)

** Total hip arthroplasty, † Total knee arthroplasty, ‡ Unicompartmental knee arthroplasty*

Efficacy compared to effectiveness

Crude LOS in the accelerated intervention group in the efficacy study was 4.9 (SD 2.4) days. Compared to that result, we observed a significant further reduction in adjusted LOS of 0.7 (95% CI 0.1 – 1.7) days, favoring the accelerated intervention in the postimplementation period ($P = 0.031$).

Quality of life

In the efficacy study, both groups reported a substantial gain in HRQOL from baseline to 3-months follow-up. The gain in HRQOL was 0.42 (SD, 0.31) in the intervention group, and 0.26 (SD, 0.31) in the control group.

We observed a significant unadjusted crude difference in gain of HRQOL at follow-up of 0.16 (95% CI 0.02-0.29) favoring the intervention group (P = 0.021). The adjusted mean difference at follow-up, likewise, yielded a significant difference in gain of HRQOL of 0.08 (95% CI 0.004-0.16) in favor of the intervention group (P = 0.028) (Table 6).

A total of 28 of 45 patients were classified as well (at or above the observed age adjusted HRQOL for the Western Danish population) in the intervention group, and 15 of 42 patients in the control group at 3 months follow-up (THA 19/28 vs. 9/28, TKA 8/15 vs. 6/12, UKA 1/2 vs. 0/2. This lead to a NNT of 3 (95% CI 2-11) for the new accelerated intervention compared to the current ntervention.

Table 6. Unadjusted, crude and stratified mean health related quality of life (HRQOL) with standard deviations. Mean, and median difference with 95% confidence interval between the accelerated and the current intervention group at 3-month follow-up, and gain from baseline to follow-up. Adjusted mean difference in gain in quality of life from baseline to 3-month follow-up, for 87 hip and knee patients, Denmark 2006

Group	Accelerated intervention	Current intervention	Difference*	*P* value
Unadjusted HRQOL				
Crude (n)	45	42		
Follow-up	0.87† (0.15)‡	0.79 (0.20)	0.08§ (0-0.16)	0.003‖
Gain	0.42 (0.31)	0.26 (0.31)	0.16 (0.02-0.29)¶	0.021**
Stratified HRQOL				
THA (n)	28	28		
Follow-up	0.88 (0.17)	0.76 (0.23)	0.13 (0-0.19)	0.001
Gain	0.44 (0.33)	0.27 (0.34)	0.16 (0.2-0.35)	0.074
TKA (n)	15	12		
Follow-up	0.86 (0.11)	0.86 (0.09)	0 (-0.07-0.08)	0.964
Gain	0.42 (0.28)	0.26 (0.25)	0.16 (-0.06-0.37)	0.142
UKA (n)	2	2		
Follow-up	0.85 (0.21)	0.80 (0.06)	0.05 (-0.13-0.25)	0.317
Gain	0.18 (0.17)	0.13 (0.16)	0.05 (-0.75-0.65)	0.793
Adjusted††				
Follow-up			0.08 (0.01-0.16) ‡‡	0.028

** Difference: HRQOL accelerated group – HRQOL current group, † Mean, ‡ Standard deviation, § Hodges-Lehman median differences with 95% confidence interval, ‖ Difference between groups tested with Nonparametric equality-of-medians test, ¶ Mean difference with 95% confidence intervals, ** Difference between groups tested with Two-sample t test, ††Multivariate linear regression including randomization group, HRQOL at baseline, gender, age, diagnosis, implant type, and randomization stratification, ‡‡ Mean difference with 95% non-parametric confidence interval based on 1000 bias-corrected and accelerated bootstrap replicates*

Adverse effects

In the efficacy study, one THA patient in the control group died perioperatively on the day after surgery because of a pulmonary embolism.

Three patients were re-admitted to hospital, within 3 months of discharge. The additional LOS after discharge was not included in the estimation of perioprative LOS for these three patients. In the control group, one TKA patient was re-admitted because of wound infection. This patient finally had to undergo revision surgery, which resulted in an additional LOS of 15 days. In the intervention group two patients were re-admitted, one TKA patient had an additional LOS of 11 days because of swelling and pain in the knee, and one THA patient had an additional LOS of 1 day because of dislocation of the hip. The LOS from these two patients led to a total additional LOS of 12 days in the intervention group.

In the effectiveness study, no significant difference in mortality was observed, as only 1 patient, a THA patient, died within 3 months after the operation in the pre-implementation period, and only 1 patient, a TKA patient, died within 3 months after the operation in the post implementation period (P = 1.0).

Likewise no significant difference in number of patients readmitted within 30 days was observed. Five of 63 THA patients were readmitted in the pre-implementation period, and 3 of 76 THA patients were readmitted in the post implementation period (P = 0.472). Only 1 of 42 TKA/UKA patients was readmitted in the pre-implementation period, versus of 3 out of 66 TKA/UKA patients in the post-implementation period (P = 1.0).

Efficiency

Costs

Average total cost in the current intervention group was US$ 14,299 (SD, 7,524), and US$ 11,306 (SD, 6,332) in the accelerated group. Average costs for the THA and TKA/UKA patients in the seven cost activity centers are presented in Fig. 10. The incremental average total cost from the univariate analysis was US$ -2,993 (95% CI, -

301 – -6,048) in favor of the accelerated intervention (*P*=0.036). The incremental average cost from the multivariate analysis was US$ -2,867 (95% CI, -1,110 – -5,522) (*P* = 0.004).

The average total cost for the THA patients was US $ 13,896 (SD, 6,326) in the current intervention group, and US $ 11,377 (SD, 6,584) in the accelerated intervention group. The incremental average total cost for THA was US$ -2,518 (95% CI, 900 – -5,770) favoring the accelerated intervention. The average total cost for the TKA/UKA patients was US $ 15,118 (SD, 9,714) in the current intervention group, and US $ 11,199 (SD, 6,091) in the accelerated intervention group. The readmitted TKA patient in the current intervention group underwent resurgery, leading to an average follow-up hospital cost of US$ 1,265. The incremental average total cost for TKA/UKA was US$ -3,918 (95% CI 873 – -10,300) favoring the accelerated intervention. No significant interaction between the intervention groups and the randomization stratification groups were identified (*P*=0.732).

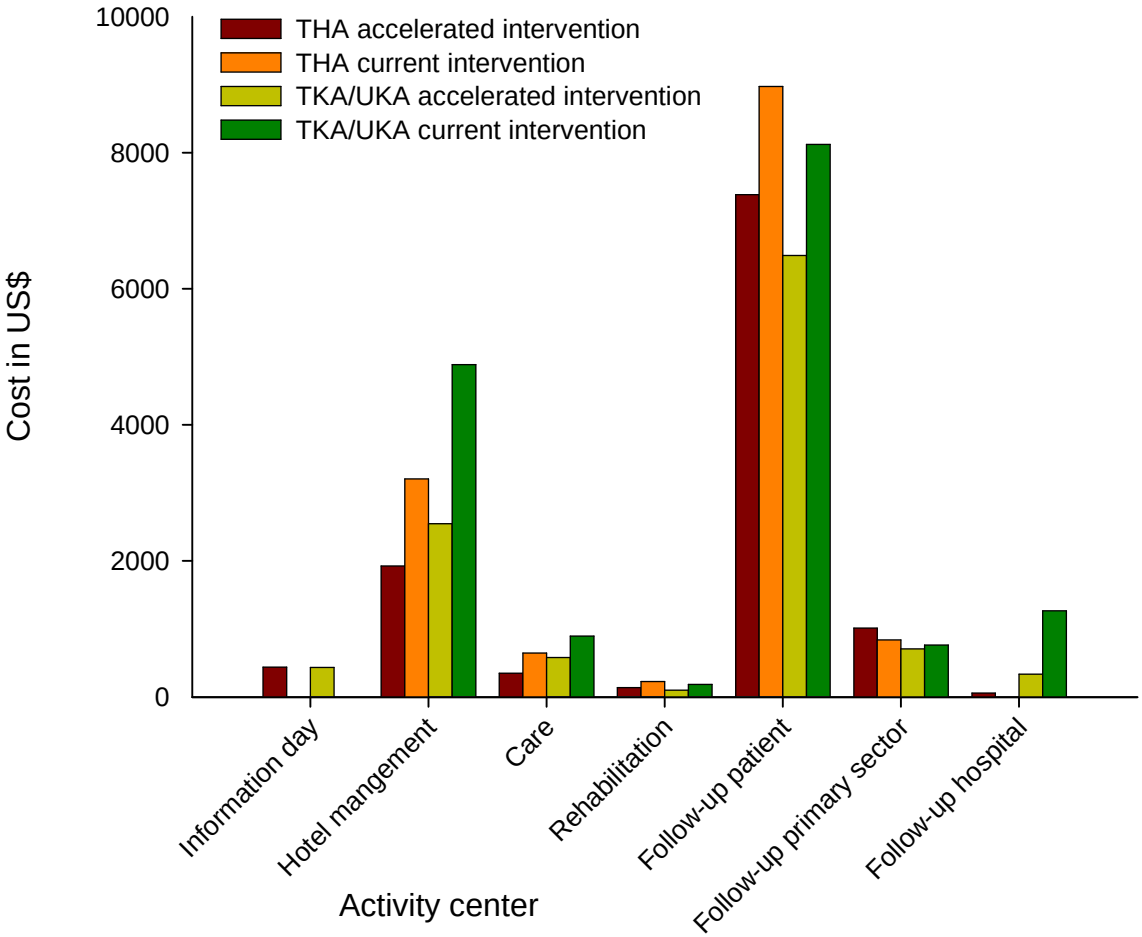

Fig. 10. Total costs in US$ in 7 activity centres for 87 patients in 4 groups receiving total hip (THA), total knee (TKA), and unicompartmental knee arthroplasty (UKA), Denmark 2005-2006

Effect

HRQOL increased on a weekly basis from the first week postoperatively and peaked at different times in the four treatment groups (Fig. 11).

Average QALY in the current intervention group was 0.78 (SD, 0.15), against 0.83 (SD, 0.10) in the accelerated intervention group. The univariate analysis revealed an incremental effect in QALY of 0.05 (95% CI, 0.01 – 0.12) favoring the accelerated intervention (P = 0.029).

For the THA patients, QALY was 0.75 (SD, 0.18) in the current intervention group, against 0.84 (SD, 0.11) in the accelerated intervention group.

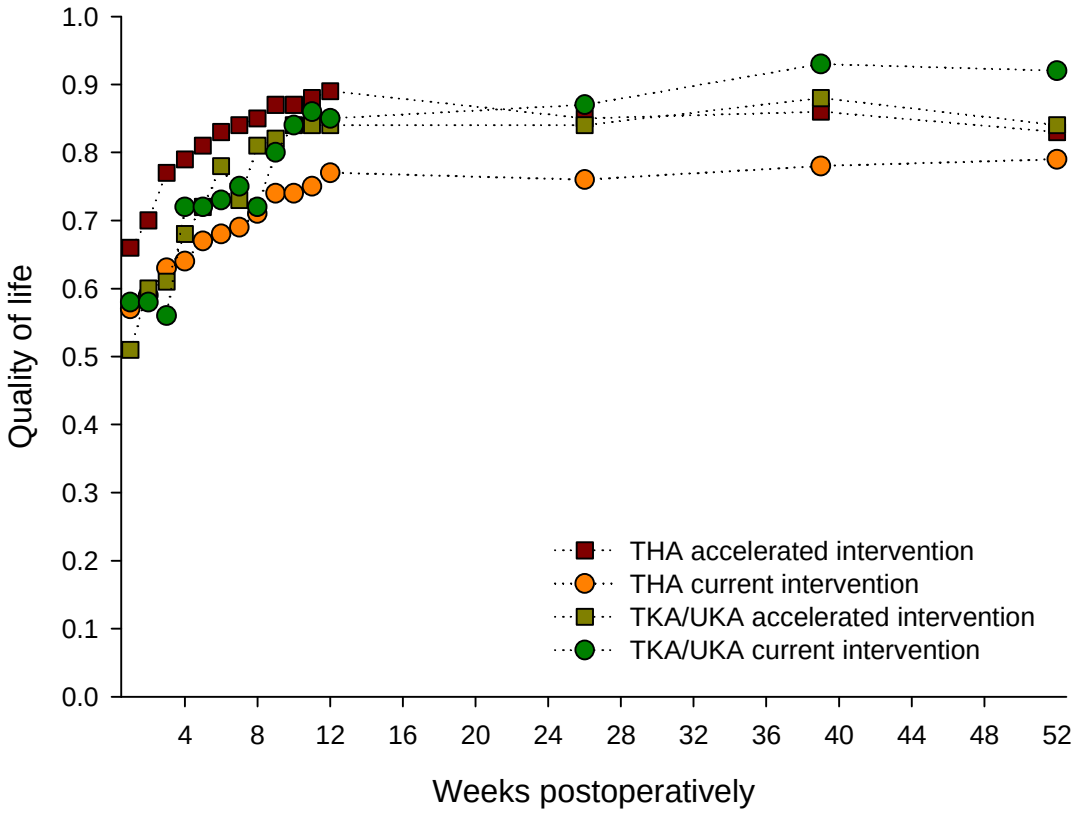

Fig. 11. Health related quality-of-life (HRQOL) measured from 15 points in time for 87 hip (THA) and knee (TKA/UKA) in four groups the first year postoperatively, Denmark 2005-2006

For the TKA/UKA patients QALY was 0.85 (SD, 0.05) in the current intervention group, and 0.81 (SD, 0.09) in the accelerated intervention group. A significant interaction between intervention groups and randomization stratification groups was observed (P=0.042).

The univariate analysis for THA patients revealed an incremental effect in QALY of 0.09 (95% CI, 0.03 – 0.18) favoring the accelerated intervention (P = 0.007). The multivariate analysis for THA patients revealed an incremental effect in QALY of 0.08 (95% CI, 0.02 – 0.15) favoring the accelerated intervention (P = 0.006).

No significant or clinically relevant difference in QALY was observed for TKA/UKA patients.

Cost-efficacy

Because of a significant interaction between treatment groups and randomization stratification groups regarding effect, the cost efficacy analyses are presented separately for the THA and TKA/UKA patients. For the THA patients, the accelerated intervention dominated the current intervention, being both significantly less costly and significantly more effective (Fig. 12). Result from a bootstrap sampling of 2000 replicates showed that 93% of the cost-efficacy pairs were placed in the lower right corner of the cost-efficacy plane. For the knee patients, we observed a less costly result for the accelerated intervention, but no significant difference in effect (Fig. 12).

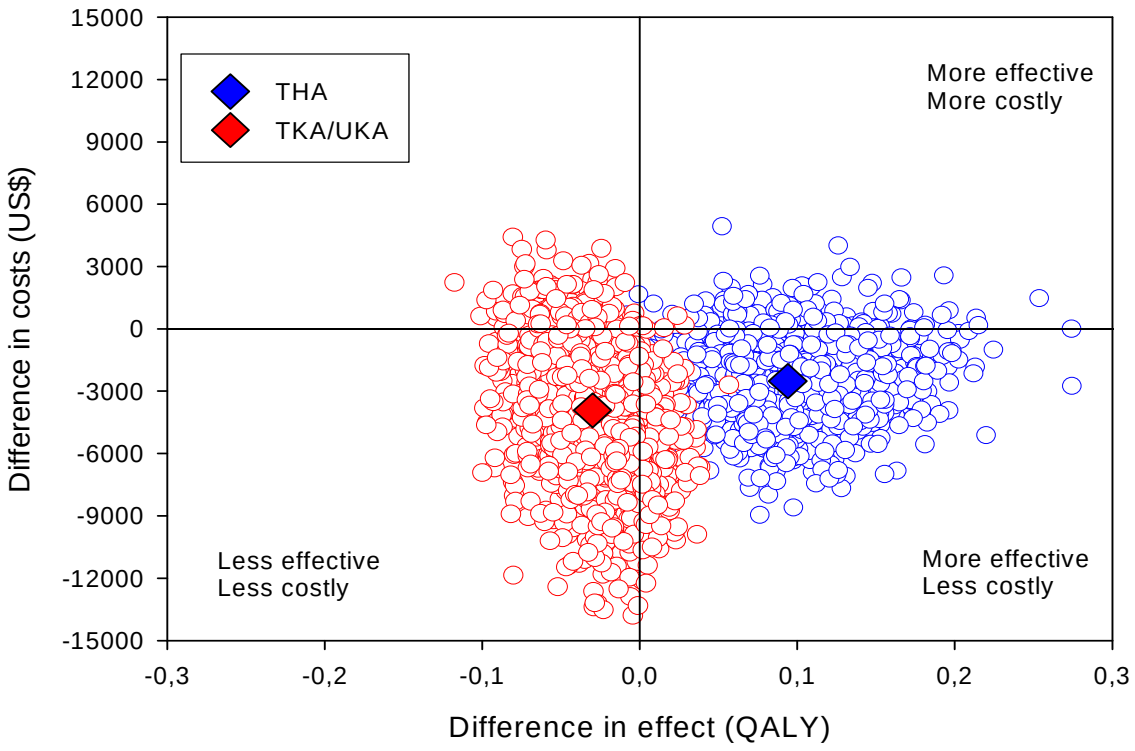

Fig. 12. Cost-efficacy plane with incremental cost-efficacy ratio (ICER) and uncertainty around the ICER from 2000 bootstrap replicates in a stratified univariate analysis of 87 patients receiving THA, TKA/UKA, Denmark 2005-2006. The cost-efficacy plane is constructed from the crossing of the X axis and the Y axis. Incremental effect is plotted on the X axis and incremental cost on the Y axis. The four resulting quadrants represent the potential outcomes in cost and effect. In the upper right quadrant the new intervention is more effective but also more costly than the comparator, in the lower right quadrant it is both more effective and less costly, in the lower left corner it is less effective and less costly, and finally in the upper left quadrant it is both less effective and more costly.

Result from the bootstrap sampling showed that 92% of the cost-efficacy pairs were placed in the lower half of the cost-efficacy plane.

Sensitivity analysis

Irrespective of analyses models or cost estimates, the results consistently favored the accelerated intervention regarding costs. In the stratified analyses of costs, the incremental cost estimates differed by US$ 463 for THA patients and US$ 444 for TKA/UKA patients when comparing OLS and GLM analyses.

For the different cost estimates with exclusion of follow-up hospital costs, we observed almost no change in incremental cost for the THA patients but a large decrease for the TKA/UKA patients.

Excluding costs from productivity loss, it led to a large decrease in incremental cost for the THA patients, while the result was almost constant for TKA/UKA patients.

The multivariate analysis of incremental effect revealed that the observed overall effect of 0.05 in favor of the accelerated intervention was actually due to the THA patients with a significant incremental effect of 0.08 (95% CI, 0.02 – 0.15) favoring the accelerated intervention (P=0.006). There was no significant or clinically relevant difference in effect for the TKA/UKA patients.

Potential bias in observed results

No obvious contamination was identified in the current intervention group during the structured observation.

The observed average crude LOS in the control group in the RCT (cohort B2) was 7.8 (SD, 2.1) days. This was lower than the expected average of 8.5 days, after adjusting for time change. The observed average LOS in the concurrent control group (cohort E) was 8.7 days, as expected (Table 3). We observed a significantly shorter adjusted LOS of 0.3 (95% CI 0.1-0.5) days when comparing results obtained in the control

group in the RCT (cohort B2) with results obtained in the current intervention group in the preimplementation period (cohort A) (Fig. 6) (P = 0.015).

Representativeness

The patients who refused to participate in the efficacy and efficiency study consisted of at least two groups. One group was characterized by younger age, more often being male and having hip replacement with an uncemented prosthesis. The other group was characterized by older age with a higher proportion of females and of knee replacements (Table 2).

No significant differences between study sample in RCT and historical or concurrent control groups was identified.

Likewise, no clinically relevant differences between study sample in effectiveness study and Danish population data was found (3;5;95-99).

7. Discussion

Key findings

To our knowledge this thesis is the first to consecutively investigate efficacy effectiveness and efficiency of accelerated perioperative care and rehabilitation intervention after THA, TKA, and UKA. The thesis reveals that the new accelerated intervention can reduce LOS without an increase in adverse affects, when compared to the current intervention. The new accelerated intervention can further reduce the total costs in a societal perspective with an additional gain in HRQOL for THA patients, against the comparator. The thesis also reveals that it is possible to implement this new accelerated intervention, and that this actually does reduce LOS without increasing adverse effects.

Consideration of possible mechanisms and explanations

We believe that the observed reduction in adjusted LOS of 3.1 days between the accelerated and current intervention in the efficacy study was achieved primarily achieved because of the new nurse lead organization, which actually made the multi-disciplinary intervention function. We believe the elements from the multi-modal intervention that contributed the most to the results were the information day and the early and more aggressive mobilization, because there were no differences in operational procedures between the two intervention groups, and only minor differences regarding pain relief, nausea reduction, nutrition and elimination.

We do not know why the THA patients receiving the accelerated intervention had an increased postoperative HRQOL. Some of the result could, however, be explained by the fact that the patients were not in a sick role, they were taught to follow and achieve preset goals. This could lead to a more positive attitude where the patients were focusing more on what they could do and less of what they could not do. The early and intensive mobilization also seemed to benefit the patients probably by reducing minor deep venous thrombosis and other problems from immobilization.

The shorter hospital stay and earlier mobilization must also have led to a lesser decomposition of physical performance, and therefore also to a quicker regain of it.

In the efficiency study, the accelerated intervention was consistently less costly than the current intervention in all seven cost activity centers, except for the information day cost, which was not part of the current intervention, and the follow-up primary sector costs for the THA patients. The latter could indicate some minor degree of cost shifting from hospital to primary sector, especially to general practitioner. The observed difference in productivity loss favoring THA patients in the accelerated intervention group was not expected, but can have great importance because of an expected higher proportion of employed patients having arthroplasty in the future. If the observation is real it could be explained by a shorter convalescence in the accelerated intervention group, which is very good in line with observed higher HRQOL observed from first week postoperatively and still present one year postoperatively.

We believe that we succeeded in implementing the new intervention because we used a combination of top-down and bottom-up implementation approaches. Our combination of the Breakthrough Series and active research worked well in this local hospital. Using a partial and gradually increasing implementation seemed to be beneficial and achieved easier acceptance from different health care professions. Successfully implementation of accelerated procedures is actually the ultimate test of multidisciplinary cooperation, with more than 10 different health care professions and an equal number of different departments involved. We especially believe that having a RCT in action period 2 was greatly responsible for the observed easy and smooth implementation in action period 3. From the theory "Diffusion of innovation", people tend to accept new procedures differently, with the "late majority" and "laggers" being more skeptical (100). These two groups in the healthcare staff were more easily convinced of the benefits of the new accelerated intervention, after having observed the comparison of the new and the old intervention in their own ward.

We were a little surprised when we compared the results from our efficacy study with the results from our effectiveness study. We would have expected the average LOS in the accelerated intervention group in the efficacy study to be shorter than LOS in the post-implementation group in the effectiveness study because a best-case scenario is thought to be better than a real-case scenario. That the effectiveness result for LOS was actually significantly shorter than that in the efficacy study could be explained by several things. One explanation is that our efficacy study was actually a pragmatic randomized clinical trial and a partial implementation under relatively normal circumstances, and not a "laboratory setup". This may have impaired the ultimately achievable result, which is therefore not known. We believe, however, that most of the difference was because the accelerated intervention was offered to all patients in the effectiveness study, whereas a rather high proportion of patients were not willing to participate in the efficacy study. These non-participating patients consisted of at least two different groups, one of which was a group of younger patients receiving uncemented arthroplasties, which in our study were among those who had the shortest LOS. A fact that support this assumption it that patients who refused to participate actually had a LOS that was shorter than the control group in the RCT. The omission of the criterion for knee flexion in the postimplementation period could also explains some of the difference, because we observed a markedly lower LOS for TKA in the accelerated intervention group in the RCT compared to the accelerated intervention group in the postimplementation period.

Comparison with relevant findings from other studies

Efficacy in a hospital and patient perspective

Since 2004, we have identified further two RCT´s of accelerated perioperative interventions, the study by Reilly et al. 2005 (101), and the study by Petersen et al. 2006 (102). Regarding the effect of accelerated intervention on LOS, the results of our study are in accordance with the study by Reilly et al. 2005 (101). They used at "true" accelerated intervention, comparable to ours, for UKA, and showed a significant reduction in LOS of 2.8 days (101). Our results are also in accordance with the study by Dowsey et al. 1999 who showed a significant, average reduction in LOS of 1.5

days for THA and TKA, when using a clinical pathway (27). Our results are likewise in accordance with the study by Munin et al. 1998 that showed a significant, average reduction in LOS of 2.8 days for THA and TKA, when comparing early inpatient rehabilitation with later (68). Our results are, however, in conflict with the study by Petersen et al. 2006, which could not demonstrate a reduction in LOS for THA, when using a multimodal intervention (102). However, none of the three latter studies used accelerated interventions as defined by us.

We believe, however, that we could have reached an even shorter LOS for TKA if we had not had the criterion for the patients to be able to reach 90° of knee flexion before discharge. Omission of this criterion is in accordance with the Danish Health Technology Assessment (HTA) report published in 2006 (99).

Our result on LOS was robust enough to show a significant effect of a "true interventional part" of the study, excluding the observed LOS before surgery.

None of the above mentioned RCT´s used HRQOL as an outcome measure. Our results are, however, in accordance with the non-RCT by Brunenberg et al. 2005 (91), which was the only study we could identify that used HRQOL as an outcome when investigating the effect of accelerated intervention compared to current intervention. They used a comparable intervention, but a before-after design. Their results regarding difference in gain in HRQOL from baseline to 3 months follow-up between the two interventions were of the same size as our. They showed a clinically relevant, but non-significant difference in HRQOL at follow-up in favor of the accelerated intervention.
We observed altogether adverse effects in 4 patients, 1 death and 3 readmissions. This is in accordance with reporting from other Danish hospitals (99).

Effectiveness in a hospital and patient perspective

The observed reduction in LOS from pre- to post-implementation in our effectiveness study is in accordance with other Danish effectiveness studies, and the Danish HTA

report from 2006 (99;103-105). Our proposed definitions for super-accelerated, accelerated, semi-accelerated and non-accelerated intervention are in line with the definition used in the HTA report for THA and TKA (99).

Have we now reached the limit with our implementation regarding LOS after accelerated procedures for THA and TKA? Apparently not, because the study by Walter et al. indicates that it could be possible to super-accelerate the convalescence of these patient groups because they reported an average LOS of 3.2 days for THA patients and 3.0 for TKA patients by using a newly designed clinical pathway (106). But on moving from accelerated to super-accelerated procedures, we have to be extremely cautious because of serious early postoperative complications (107).

The observed number of complications in our effectiveness study is also in accordance with a comparable publication, in which a tendency towards fewer complication for hip patients and more complications for knee patients is reported (99). However, there is a risk to accelerate the pathway too much, as a very high readmission rate of 13% within 30 days was reported from the hospital which reached the shortest LOS, and an overall higher readmission rate was observed for the knee patients receiving the accelerated procedures (99). We believe the reporting of any readmission to be the best measure for comparing adverse effects of too early discharge, as it is not affected by misclassifications in coding of complications. We therefore appeal to focus even as much on adverse effects, such as perioperative infections, implant dislocation, and any readmission, as LOS when implementing accelerated procedures.

Efficacy compared to effectiveness

The differences we observed between the results for LOS from the efficacy and the effectiveness study could indicate that there are some problems in extrapolating results from RCT´s with high proportions of refusing patients to the target population. This observation is in accordance with Petersen et al., who along with others, have questioned the results from RCT´s with rather large proportions of non-participating patients (108). The difference in results between the two study designs could not be explained by a mere extension of the accelerated intervention from the

efficacy to effectiveness study, because the entire leading health care staff and most of the other health care staff differed between the two study periods. Moreover the new healthcare staff had to adopt the new multi-modal intervention. However, although there are some problems, we still need to evaluate results from both efficacy and effectiveness studies before completely accepting a new intervention. But special care must be taken in the future to minimize the proportion of non-participating patients in efficacy studies, because we could else miss the ultimately achievable results that we later on should stride for when we monitor effectiveness and efficiency.

Efficiency

Cost-efficacy

Regarding the costs of the accelerated intervention, our study is in accordance with the only other study we could identify on this topic (91). In that study, the authors used a similar intervention, but in a before-after design. A difference between preoperative costs in the two studies is seen, but they included more cost areas than we did, because we assumed most preoperative cost differences to be controlled through the randomization. Our study also demonstrated much higher postoperative costs in both groups, primarily explained by a larger productivity loss from a greater proportion of employed patients. The incremental costs in both studies favored the new, accelerated intervention, although this was more pronounced in our study.

Compared with Brunenberg et al. (91), we observed a much higher QALY in our study for all four patient groups, at all five comparable time points. Some of this difference could be explained by different indications for surgery because in Denmark surgery is associated with less pain and disability. This seems to be in accordance with best practice, i.e. the lower the preoperative QALY, the worse the postoperative results (109). Another explanation for the higher QALY is that we observed a much greater proportion of patients still being employed and active than reported in the study by Brunenberg et al. (91). It is, however, not known whether the proportion of employed patients observed in our study is representative for the general Danish patient population. In a multivariate analysis, Brunenberg et al. demonstrated a clinically relevant, but non-significant incremental effect in QALY of

0.05, favoring THA patients (91). We likewise demonstrated a significant incremental effect of the same magnitude. However, because this positive finding was not obtained from a study, in which sample size was calculated using QALY as a primary outcome measure; this result has to be demonstrated in another study in which this issue is the primary research question. In both studies, no significant difference in QALY between the two groups of knee patients could be identified.

Brunenberg et al. demonstrated that accelerated intervention was superior to the current intervention for both THA and TKA patients (91). We were only able to demonstrate an advantage for THA patients and a significantly less costly intervention for TKA patients. We do not know why this difference between Danish and Dutch TKA patients occurs, but it could be explained by the generally lower QALY from baseline to 1-year follow-up, probably due to different indications for surgery. Danish TKA/UKA patients reach a state of health 1 year postoperatively in both the current and accelerated groups that was above the gender- and age-matched Danish population, while Dutch TKA patient reach a level far below the gender- and age-matched Danish population (59).

Cost-effectiveness

Because no cost data was collected alongside the effectiveness study, it is therefore still uncertain if cost-effectiveness could be demonstrated in a Danish population during routine circumstances. However, as most of the observed cost difference between the two interventions in the efficacy study was due to a difference in perioperative costs obtained through a shorter LOS in the accelerated intervention group, it is most likely that a further reduction in LOS observed in the effectiveness study will also lead to cost-effectiveness in a Danish population. This in line with the observed results obtained for semi-accelerated interventions for THA and TKA (99).

Limitations

Selection bias

We believe that our great attempts to minimize selection bias in the efficacy and efficiency studies were mostly successful.

In the efficacy and efficiency studies, we used consecutive inclusion, broad inclusion criteria and only excluding patient who were mentally and severely physically disabled. Fever than 5% of the eligible patients were excluded. However, a rather high proportion of patients refused to participate. Those patients who refused participation fell into two groups. One group, young male patients going to have an uncemented hip implant, could easily be accelerated. The other group, elderly women going to have knee replacement would probably be more difficult to accelerate. But we expect that these two groups on average would perform as well as those who were included. An indication of this is that the patients in the intervention group in the effectiveness study, where all patients were included, actually showed better results for LOS. Furthermore concurrent and historical control groups showed that our sample was representative for the study population regarding sex, age, diagnosis, and implant type, which we consider the most important when describing case mix.

In the effectiveness study all patients were included, and the question is then if these patients represent the Danish population of elective primary THA, TKA, and UKA patients. We could, however, not identify any clinically relevant differences in case mix or other areas for THA and TKA/UKA when compared to Danish population data (96;98;110).

Information bias

We believe to have succeeded in reducing information bias in all three studies though our choice of data collection, methods for masking of participant, choice of outcome and endpoint.

Data collection

We used register data and questionnaires for all data collection. We consider the quality of our data obtained from registers to be good, since all data used were obtained from available official Danish registers, which have been in use for several years, and had been through some form of validation process (57). The questionnaire we chose is widely used and has been through an extensive validation process (53;58).

Masking of participants

We believe our attempt to mask the patients and the healthcare staff in the efficacy and efficiency studies were mostly successful. However, the result for LOS in the control group in the efficacy study, in which patients and health care staff were aware of being under study, was significantly lower than that observed in the effectiveness study, in which they were not aware of being under study. No obvious contamination in the control group in the RCT was identified from the observational study. Therefore, after having ruled out contamination in the control group in the RCT, we believe that the observed difference in LOS between the control group in the RCT and the current intervention group in the preimplementation period was due to a Hawthorne effect. An unintentional effect in the control group is in accordance with that observed in the study by Dowsey et al. 1999, where they report a large reduction in LOS in both the intervention and control groups compared to the period just prior to the study period (27).

Outcome

Although LOS is a legitimate outcome it is still rather problematic to use LOS as an outcome, as it is also part of the accelerated intervention. We therefore emphasize, that LOS cannot be regarded as a single primary outcome, but must be seen in relation to other outcomes, such as we have done using HRQOL and adverse effects. We believe the best way to handle LOS, is to calculate costs for perioperative LOS as well as readmission LOS and then use this in a societal perspective, as we have done in the efficiency study. However, most importantly is to keep discharge criteria unchanged (23). We believe that our discharge procedures were identical in both

intervention groups during the entire study period, except from intended omission of the criteria of knee flexion for TKA in the postimplementation period.

We believe our choice of HRQOL as an important outcome is supported by the fact that it was proposed by international health organizations to be useful in quantifying the burden of musculoskeletal diseases (50;51). We chose to use EQ-5D to measure HRQOL because it has been found useful for monitoring the included patient groups (7).

Using mortality, complications and readmissions as outcomes alone is also not feasible in smaller studies like these because events are rather rare. The best way to deal with this is therefore in large registers.

Endpoint

We chose an endpoint of three months in the efficacy and the effectiveness studies, because this was the usual time for terminating treatment and normally no further follow-up visits or contacts were planned from the hospital. We have documented the choice of endpoint to be fair, as very little change in HRQOL takes place after this point. In the efficiency study we also believe that we have collected most relevant costs and effects with a follow-up time of one year.

Analysis bias

We believe we have succeeded in minimizing analysis bias by fair sample size, relevant comparator, relevant analysis perspective, and adjusting for most known and unknown confounders.

Sample size

In both the efficacy and the effectiveness study our sample size calculation was based on available data. However, choosing a power of 0.8 in the efficacy and efficiency study could have resulted in a type II error. Because of an unknown interaction between randomization stratification group and intervention groups our sample size proved to be too small for stratified analysis, especially for the TKA/UKA patients.

Because the efficiency study was a piggy-back study to the RCT no separate sample size calculation was made for that study, except from expected cost reduction from reduced LOS. This made it impossible to test differences between the different cost areas, which could have been of interest.

Choice of comparator

The purpose of the current thesis was to investigate the efficacy, effectiveness and efficiency of accelerated perioperative procedures, and in order to do that you need a comparator. Our choice of comparator was the current intervention at our local hospital. Because we do not know to what extent this intervention is representative for procedures performed in other Danish hospitals, perhaps this is the greatest limitation for extrapolation the results to other orthopedic clinics. However, we observed the result for LOS in 2004 for the orthopedic clinic Regional Hospital Holstebro to be close to the average for all public Danish hospitals.

Perspective of analysis

The consecutive analysis of efficacy, effectiveness and efficiency secured that all relevant perspective was analyzed (i.e. the hospital, the patient and the societal).

Adjusting for confounders

In the efficacy and efficiency studies, our analysis of LOS and HRQOL included adjusting for the most common confounders, as well as the randomization stratification in order to get the most precise estimate of the effect of an accelerated intervention. We observed a markedly difference between the result from the unadjusted and the adjusted analysis of HRQOL gain, indicating, that future studies of HRQOL or quality adjusted life year (QALY) must take baseline differences in group characteristic into account.

In the effectiveness study we adjusted for the most important case mix factors (gender, age, diagnosis, procedure and patient group).

Choice of analysis model

The result from our univariate analysis in the efficiency study showed the accelerated intervention to be almost US$ 3,000 less costly than the current intervention, with an additional gain in QALY of around 0.05. In accordance with the recommendations of Glick et al. (92), we also performed a multivariate analysis together with different analysis models including OLS and GLM analysis, and different cost estimates to provide the reader with a degree of variation in the estimates due to model and estimate uncertainty. The results from these analyses did not change the overall conclusion, but markedly changed the estimates. The multivariate analysis identified a significant interaction between randomization stratification groups and intervention groups, indicating that a stratified analysis would be the most appropriate. In the stratum specific analysis, the results from the univariate analysis seemed to have overestimated the incremental costs for the THA patients, whereas stratum specific analysis underestimated the results for the TKA/UKA patients compared with the multivariate analysis. This tendency was more pronounced using GLM analysis, and the incremental cost estimates differed as much as US$ 463 compared to OLS, indicating that there is some difference in cost estimate based on choice of analysis model. Analyzing cost estimates not including readmission costs did not affect the results for the THA patients, whereas this highly affected results for the TKA/UKA patients because of one readmitted patient in the current intervention group, who had to undergo resurgery. For the THA patients, about half of the incremental cost was explained by different productivity loss in the two intervention groups. The TKA/UKA patients had a different pattern regarding productivity loss, mostly due to a lower general proportion of employed, but also because of a different proportion of employed in the control and intervention group. In the stratum specific analysis of effect, the results favoring the accelerated intervention were solely due to an effect gain by the THA patients. Our results therefore demonstrate the usefulness of different analysis models and estimates of transferability.

We did not present a cost-efficacy acceptability curve, which shows the probability that the accelerated intervention will be cost effective, depending on what the society

is willing to pay per QALY gained, or results using the net-benefit framework, because they have little or no relevance in situations where one intervention dominates the comparator or when one intervention is less costly and has the same effect as the comparator.

When we estimated the reduction in LOS between groups in the effectiveness study, we used multivariate analysis in order to adjust for potential differences in the most important covariates to get the most precise estimate. Although there were no significant differences between the patient characteristics in the two groups, there was still a trend toward an increased proportion of TKA patients and of THA patients receiving an uncemented implant. Furthermore, UKA was introduced as a new intervention in the post-implementation period.

Generalizability

We believe the investigated patient sample in the efficacy and efficiency study was representative for a regional population, and the sample in the effectiveness study was representative for the case mix in most other Danish public hospitals.

One of the strengths of our studies is that they were performed by using a pragmatic design in a local hospital, and not with highly selected patients and health care staff in a University hospital. We therefore believe that our interventions could be widely implemented, and that similar results could be reached in most other hospitals, and for the society as a whole.

8. Conclusion

In this PhD thesis we have documented that an accelerated perioperative care and rehabilitation intervention is effective compared to the current intervention, in patients undergoing primary total hip, total knee, and unicompartmental knee replacement, in a hospital and patient perspective. An accelerated perioperative care and rehabilitation intervention is also shown to be cost effective compared to the current intervention, in a societal perspective. We have finally described a successful implementation process, documented that it was possible to half the average length of stay from one year to another without adverse effects, and that effectiveness could actually match efficacy in this population.

9. Perspectives and future research

Perspectives

The studies presented in this thesis demonstrate that accelerated interventions can be implemented with positive results for both hospitals and patients. We hope our studies have contributed to a higher evidence of accelerated procedures for THA, TKA, and UKA and that it can lead to stronger recommendations of implementing these procedures. If perioperative interventions comparable to ours are implemented in all Danish hospitals it could lead to a yearly freeing of as many as 35,000 hospital bed days, which has a yearly value of more than DKK 200.000.000, and an additional gain of approximately 500 QALY.

Furthermore we believe that when accelerated intervention has been implemented in one are in a hospital it will be easier to spread the concept of a multi-disciplinary organisation and a multi-modal intervention to the pre- and postoperative period, to other fields of orthopaedic surgery and other fields of elective and acute healthcare interventions.

Future research

There is still some way to go before we have developed the ideal intervention for THA, TKA, and UKA. We are, however still contributing with research in this area. We are currently performing studies that investigate the reliability and validity of patient administered versions of Harris Hip Score and Knee Society Clinical Raring System. If the outcome measures prove to be valid and reliable, they will be used in a planned cost-effectiveness study. We are also performing a Markov-model study of TKA versus UKA for a Danish population, in order to investigate how much the higher revision rate for UKA affects costs-effectiveness between these two interventions. We are finally performing studies that investigate optimization of the pre- and postoperative period in order to know how much the different element contribute to the overall result.

We together with others are also focusing on optimization of perioperative pain relief, which together with preventive treatment of deep venous thrombosis should be rethinked in the context of accelerated procedures.

We finally believe that there should be much more focus on collecting reliable, valid and complete cost and effect data at the patient level for DHAR and DKAR in order to monitor effectiveness of interventions for THA, TKA, and UKA. SHAR and SKAR have proven this to be possible.

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12. Appendices

Appendix 1.

Search strategy for identification of studies to establish efficacy, effectiveness, and efficiency

We sought relevant studies in the following databases: the Cochrane Central Register of Controlled Trials, Cochrane Musculoskeletal Group Trials Register, MEDLINE, CINAHL, EMBASE. All searches were performed up to December 2004. In addition, we searched reference lists of articles presented in Danish hip and knee reference programs and Danish year reports, related articles of included studies, and in Ugeskrift Laeger [in Danish]. There were no language restrictions.

We used the following common search words for the efficacy, the effectiveness, and the efficiency studies:

Hip arthroplasty:
("hip"[MeSH Terms]
OR
hip[Text Word])
AND
("arthroplasty"[MeSH Terms]
OR
arthroplasty[Text Word])
OR
"hip replacement arthroplasty"[Text Word]
OR
"arthroplasty, replacement, hip"[MeSH Terms]
OR
hip replacement[Text Word]

Knee arthroplasty:

"knee replacement arthroplasty"[Text Word]

OR

"arthroplasty, replacement, knee"[MeSH Terms]

OR

knee arthroplasty[Text Word]

Accelerated intervention:

accelerated[All Fields]

OR

fast[Text Word]

OR

"track and field"[MeSH Terms]

OR

track[Text Word])

OR

"critical pathways"[MeSH Terms]

OR

critical pathway[Text Word]

OR

clinical pathway[Text Word]

OR

joint[Text Word]) AND care[All Fields]

OR

joint-care[All Fields]

OR

multidisciplinar[All Fields]

OR

multi-disciplinar[All Fields]

OR

multi[All Fields] AND disciplinar[All Fields]

OR

multimodal[All Fields]
OR
multi-modal[All Fields]
OR
multi[All Fields] AND modal[All Fields]
OR
multiprofessional[All Fields]
OR
multi-professional[All Fields]
OR
multi[All Fields] AND professional[All Fields]
OR
interdisciplinar[All Fields]
OR
inter-disciplinar[All Fields]
OR
inter[All Fields] AND disciplinar[All Fields]))

We further used specific filters:

In the efficacy study:
1)
"1960/01/01"[PDat]:"2004/12/31"[PDat]
AND
Meta-Analysis[ptyp]
OR
Review[ptyp]

2)
"1960/01/01"[PDat]:"2004/12/31"[PDat]
AND
Randomized Controlled Trial[ptyp]

In the effectiveness study:

1)

Danish

OR

Denmark

AND

"1960/01/01"[PDat]:"2004/12/31"[PDat]

AND

Meta-Analysis[ptyp]

OR

Review[ptyp]

2)

Danish

OR

Denmark

AND

"1960/01/01"[PDat]:"2004/12/31"[PDat]

AND

Clinical Trial[ptyp]

OR

Randomized Controlled Trial[ptyp]

In the efficiency study:

"cost-benefit analysis"[MeSH Terms]

OR

cost effectiveness[Text Word]

OR

"economics"[Subheading]

OR

"costs and cost analysis"[MeSH Terms]

OR

cost[Text Word] AND efficacy[All Fields]

OR

cost-efficacy[All Fields]

OR

"efficiency"[MeSH Terms]

OR

efficiency[Text Word]

AND

"1960/01/01"[PDAT] : "2004/12/31"[PDAT]