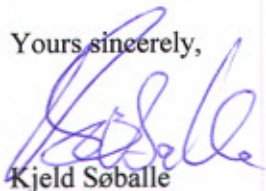


Enclosed please find the requested complete version of our application to the Lundbeck Foundation support within "Interventional Research in Clinical Medicine".

**Fast-track surgery – the case of hip and knee arthroplasty**

Yours sincerely,



Kjeld Soballe

Professor  
Århus University Hospital



Henrik Kehlet

Professor  
Copenhagen University Hospital

**Fast-track surgery - the case of hip and knee arthroplasty**


The concept of fast-track surgery was originated by Professor H. Kehlet more than a decade ago and based upon clinical research within pain physiology and treatment, perioperative care regimes including nursing care, fluid management, endocrine metabolic research, etc. and the concept has since gained widespread international interest and impact to improve outcome and decrease need for hospitalization.

The other applicant, Professor K. Søballe has conducted several randomized studies on fast-track surgery since 2000.


The present project performed in collaboration between Department of Orthopaedic Surgery and Anaesthesiology, Hvidovre Hospital, Section for Perioperative Pathophysiology, Rigshospitalet, Department of Orthopaedics, Aarhus University Hospital and Regionshospital Holstebro is seen as an extension of previous research for the involved institutes to use a single, high-volume surgical model (hip and knee arthroplasty) to provide further outcome data based on clinical interventions - studies and results that we consider to have major impact for improvement in other types of major surgery, as well.

The administrations have over the last decade observed a major improvement in perioperative outcome reflected as decreased need for hospitalization in a variety of surgical procedures as a result of fast-track studies. However, we think there is a more widespread potential based upon the results of the actual project - and confirm that all facilities (anesthesiological expertise, a high-volume hip and knee arthroplasty and specialized nursing care), all of which may provide unique possibilities for a successful project. Therefore, we will support this unique collaborative effort to be performed. Finally, the logistics and research facilities are well in place to secure the project, and the applicants have documented the ability to perform and complete major clinical research projects.

Kind regards,

  
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Proposal for a Lundbeck Foundation Centre  
within the field of interventional research in clinical medicine

# **Fast-track Surgery**

## **The Case of Hip and Knee Arthroplasty**

Establishment of a collaborative  
Centre for Fast-track Hip and Knee Surgery

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## 1 Danish summary

Behandlingskonceptet "Det accelererede patientforløb" har inden for hofte- og knæalloplastikkirurgien i flere år fungeret med succes på bl.a. Regionshospital Holstebro, Regionshospital Silkeborg, Aarhus Sygehus samt på Hvidovre Hospital. Konceptet bygger på information, motivation og logistik samt anvendelse af tilgængelige evidensbaserede tiltag indenfor alle delområder af behandling, pleje, træning, bedøvelse, smertebehandling mm. De primære resultater viser, at indlæggelsesvarigheden uden ressourcetilførsel kan reduceres til 3-4 dage – med bibeholdelse af meget høj patienttilfredshed og meget få komplikationer. Udviklingen inden for accelererede operationsforløb har betydet et meget stort kvalitetsløft i den kirurgiske behandling, en proces, der fortsat bør optimeres med henblik på den ultimative opnåelse af et »smerte- og risikofrit« operationsforløb.

I Centre for Fast-track Hip and Knee Surgery - en interdisciplinær organisation - planlægges multimodale interventioner til fortsat optimering af forløbene for knæ- og hoftealloplastik patienter omhandlende smertebehandling, transfusionsstrategi, effekt af fysioterapi, postoperativ kognitiv dysfunktion, optimeret antitrombotisk behandling, samt sikkerhedsmonitorering og evaluering af hofte-luksation og løsning af protesen. Der stiles ultimativt mod et reduceret hospitaliseringsbehov til 1-2 dage. Det skitserede forskningsprogram vil have vidtrækkende perspektiver og implementering inden for andre operationsforløb.

## 2 Background

Surgical injury is followed by pain, stress-induced catabolism, impairment of organ functions (pulmonary, cardiac, muscle) and a risk of thromboembolism. These events may contribute to complications, need for hospitalisation, postoperative fatigue and delayed convalescence and rehabilitation. In order to enhance recovery and reduce postoperative morbidity, hospitalisation and convalescence, the concept of fast-track surgery has been introduced as a multimodal intervention including preoperative optimisation of organ dysfunction/patient information, multimodal non-opioid analgesia, optimised fluid management, reduction of surgical stress responses combined with early mobilisation and oral nutrition<sup>1</sup>. The concept has proven valid in a variety of procedures<sup>1,2</sup>, most well-documented in high-risk colonic surgical patients.<sup>3</sup>

Major orthopaedic surgical procedures are performed with an increased frequency, i.e. hip and knee surgery with more than 12000/yr in Denmark, and is expected to increase further due to an increased elderly population and obesity. Presently, these major operations are followed by 5-10% morbidity and need for hospitalisation (national average ~ 6 days)<sup>4</sup>, and an ill-defined need for postoperative rehabilitation.

The first Danish description of a 6-day fast-track hip and knee arthroplasty programme was published in 1992.<sup>5</sup> The programme has since been further developed at Hvidovre Hospital and Aarhus University Hospital, and here the duration of hospital stay now is within the range of 3-4 days<sup>6</sup> (and local hospital registers) compared with the national average of about 6-8 days.<sup>4</sup>

The aim of the present study is to optimise pain management, fluid therapy,<sup>7</sup> transfusion and anti-thrombotic regimens and physiotherapy in order to achieve a reduced need for hospitalisation to 1-2 days, with reduced risk of late organ dysfunction, functional disability, pain, need of physiotherapy

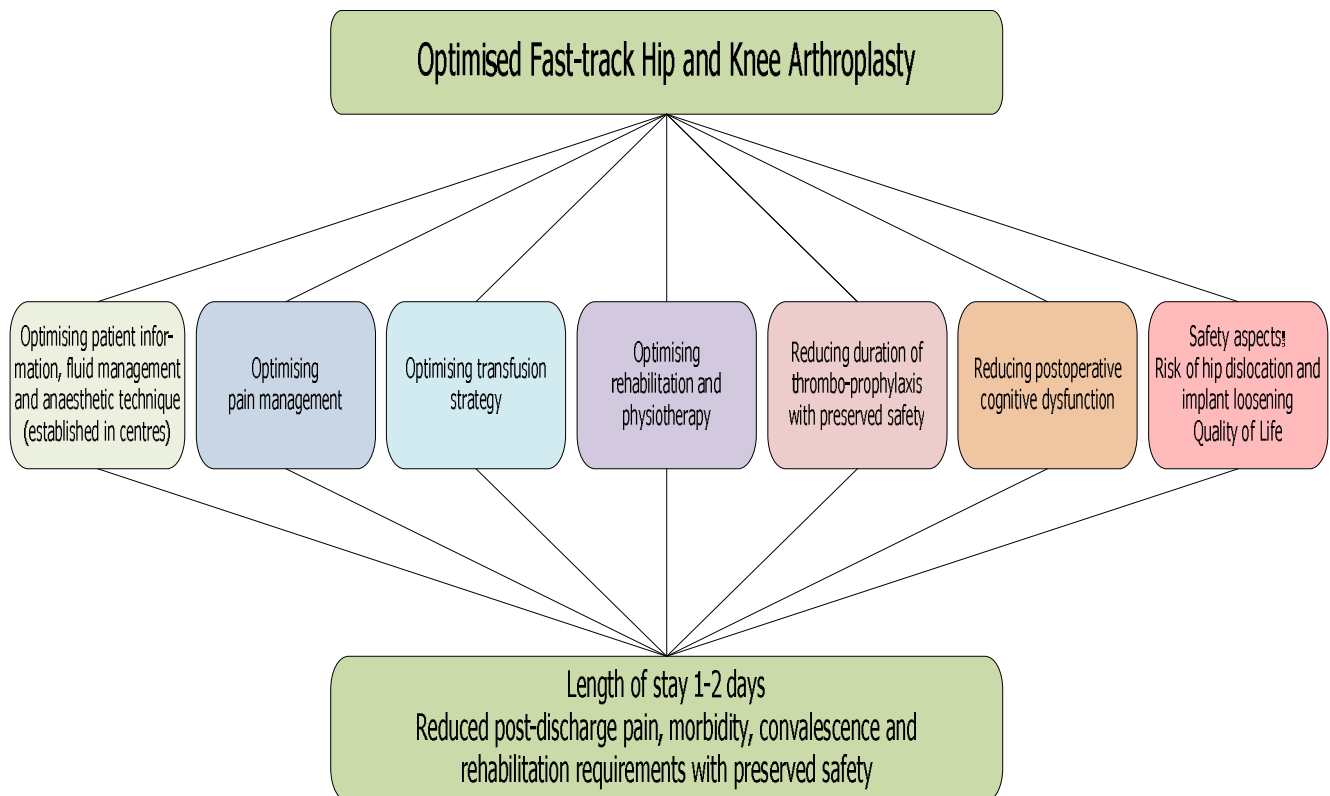
and with preserved safety (hip dislocation and prosthetic loosening) and improved patient satisfaction (quality of life).

The study programme is based on a strong collaborative research environment, by combining the expertise achieved in the orthopaedic departments participating in the Centre together with the help of experts within postoperative cognitive dysfunction, thromboembolism and transfusion. The perspectives go far beyond the two surgical procedures addressed because the results may be applicable to other orthopaedic procedures as well as major procedures in other surgical specialities.<sup>1,2</sup>

### 3 Nature and importance of the research

The projects have been selected based on the group's previous research in the field. The unifying hypothesis is that these major, relatively high-risk orthopaedic procedures can be performed with minimal pain, 1-2 days' need for postoperative hospitalisation, less cognitive dysfunction, decreased need for postoperative physiotherapy and analgesics and reduced thromboembolism/ thromboprophylaxis.

The major categories for the research programme are as follows:



### 3.1 Optimisation of perioperative pain management and implications for outcome

#### Background

Effective postoperative pain relief is a prerequisite for successful "fast-track" recovery,<sup>1</sup> and modern perioperative pain management follows the concept of "multi-modal opioid-sparing analgesia" as originally proposed by the principal investigators<sup>8</sup> and summarised recently.<sup>9</sup> Although major improvements have been achieved,<sup>1</sup> procedure-specific optimisation of analgesia<sup>10,11</sup> is still required due to a large inter-individual variability in pain perception and responses to surgery<sup>12</sup> and because of a procedure-specific variability in the risk-benefit ratio of different analgesics.<sup>10,11</sup> With regard to hip and knee arthroplasty the current evidence recommends non-opioid systemic analgesia together with peripheral blocks,<sup>10,11</sup> especially continuous femoral block techniques, in knee arthroplasty.<sup>10,11,13</sup> More recently, a new high-dose local infiltration analgesia (LIA) technique has been developed and documented to be effective<sup>14-23</sup> and probably has less side-effects (limb paralysis) than the continuous femoral block techniques.<sup>13</sup> The principal investigators have participated in five randomised trials<sup>14,16-18,22</sup> of the LIA-technique and recently summarised the future demands for understanding the mechanisms and efficiency of this simple technique<sup>21</sup> (optimal location of infiltration/catheter technique,<sup>17</sup> role of compression,<sup>18</sup> adjuvants and finally a straight-forward, double-blind randomised assessment vs. a "gold standard" continuous femoral nerve block.<sup>13,24</sup>

A specific problem in perioperative pain management is to understand the mechanisms behind the large inter-individual variability and pain perception in order to improve overall analgesic efficacy. In this context, several "pain genes" have been identified.<sup>25-27</sup> Furthermore, data from experimental studies<sup>28</sup> suggest that inflammatory mediators (especially IL-6) may play a role, including a specific role in postoperative rehabilitation.<sup>29</sup> Finally, preliminary data from other procedures suggest that the large inter-individual variability in the cytokine response to injury is related to the risk of postoperative morbidity.<sup>30,31</sup> These data open up for further efficacy and safety data on perioperative glucocorticoid treatment of pain and the inflammatory response with potential benefits for overall recovery.<sup>32-34</sup> Very little attention has been paid to post-discharge pain, which after hip and knee arthroplasties may be especially important for functional recovery and physiotherapy. Data from the principal investigators<sup>35</sup> (see fig. 1, p. 6) have shown that a significant proportion of patients have pain extending throughout the first 4-week period, calling for improvement. Also, about 10% of patients end up in a state of persistent postsurgical pain.<sup>36,37</sup>

#### Study hypothesis

The study set-up with the pre-existing "fast-track" hip and knee arthroplasty group and documented pain expertise in the research centres will provide a unique opportunity to clarify the following clinical relevant issues:

- A. To develop the "optimal" multi-modal plus continuous LIA technique in hip and knee arthroplasties<sup>21</sup> compared with the existing "gold standard" of peripheral nerve block,<sup>10,13,24</sup> the latter being more difficult and with an assumed high risk of side effects.

#### Study design:

1. In randomised trials (based upon previous power calculations<sup>16-18</sup> to assess the differential analgesic effect between intracapsular and intraarticular local administration after knee arthroplasty.

2. In a similar-sized randomised trial to assess the relative analgesic effect of intracapsular vs. subcutaneous local anaesthetic administration after knee arthroplasty.
3. To evaluate the role of single- vs. multihole catheter on the spread of local anaesthetic in the surgical wound, using a  $^{99m}\text{Tc}$ -DPTA scanning technique, as previously used by the investigators in epidural analgesia.<sup>38</sup>
4. A dose-volume relationship study on the analgesic efficacy of continuous wound infusion after total knee arthroplasty (catheter type and location depending on 1, 2, and 3)
5. To perform a final double-blind, randomised study (n = 100) on the analgesic efficacy and safety of continuous wound infusion of local anaesthetic compared with previous "gold standard" continuous femoral nerve block.<sup>13,24</sup> Catheter type and location depending on results of 1-4.

6-8 Similar studies, design, and number of patients but after hip arthroplasty.

Summarising, the research plan will for the first time in a systematic fashion define the optimal technique of using the otherwise promising technique of wound infusion of local anaesthetic, the hypothesis being that this will replace the previous "gold standard" continuous femoral block technique, which is more demanding of expertise and has demonstrated side-effects, including muscle weakness.<sup>13</sup> The planned studies will include wound infusion for 2-4 days after discharge.<sup>13</sup>

- B. To document the effects and safety of preoperative, high-dose glucocorticoid administration to modify the inflammatory response, pain, and functional outcome, as suggested from preliminary observations.<sup>32,33,39</sup>

Study design:

1. An initial small-size, double-blind, randomised study to assess the efficacy of preoperative methylprednisolone 125mg vs. placebo on acute and sub-acute (up to 30 days) pain, inflammatory responses (CRP and IL-6), fatigue, sleep quality, and well-being, based on the research group's previous experience with other procedures<sup>33 35</sup> (N=60), with power calculation based on previous studies<sup>16-18</sup>
2. A similar study in knee arthroplasty
- 3-4 Based upon the results of 1 and 2, to perform two large (n=200 each), randomised studies with the same parameters as 1 and 2, but including detailed functional scores (see physiotherapy section) up to 6 weeks postoperatively, including safety aspects<sup>33</sup>
- C. To optimise post-discharge multimodal pain treatment to decrease the percentage of patients with moderate to severe pain from ~50% to ~20% within the first 4 weeks<sup>35</sup> (see fig. 1, p. 6) to provide an improved setting for enhanced rehabilitation.

Study design:

1. Based on the previous findings of significant pain, despite previous local infiltration techniques<sup>21,35</sup> and with 7 days of postoperative treatment with gabapentin, paracetamol, and a COX-2 inhibitor, to decrease the undesirably high pain levels within the first 4 weeks after discharge<sup>35</sup> (see fig. 1, p. 6). These studies with the same power calculations as in B will be performed after the results of study 1 in B, but with additional gabapentin, paracetamol, and COX-2 inhibitor for 4 weeks in



combination with a slow-release opioid, which has less side-effects in the early acute pain phase.<sup>9</sup> This will be the first ever trial to assess the effect of multimodal analgesia during a prolonged postoperative period during which functional recovery and participation in physiotherapy will be assessed in detail (see physiotherapy section).

- D. To define the role of inflammatory mediators (plasma CRP and IL-6, and SNP (PCR): TNF- $\alpha$ 208, IL-10 627, IL-6 174<sup>40-42</sup> assessed pre- and postoperatively), pain genes (predominantly COMT genes, GTP cyclohydrolase and tetrahydrobiopterin-related genes<sup>25-27</sup>) on acute and sub-acute (4 weeks) and late (6 months) pain as well as functional recovery (see physiotherapy section). Preoperative prediction of pain response will make possible giving aggressive analgesic therapy to high pain responders and less aggressive therapy to those with a lower pain disposition. Furthermore, prediction will allow improved design of future analgesic studies by only including high pain responders.

Study design:

1. These large, consecutive cohort series (n=200 in knee arthroplasty, and n=200 in hip arthroplasty) will be the first ever to define which patient populations can be expected to be high pain responders<sup>35</sup> with a potential risk for chronic pain<sup>37</sup> in relation to genetic disposition to inflammatory and anti-inflammatory responses as well as to the pain genes.
- E. To analyse in detail, based upon A, B and D "why is the patient still in hospital today?"

Study design:

1. We hypothesiise that the results of A, B, and D will decrease the need for hospitalisation to 1-2 days. Consequently, we plan to perform a detailed consecutive study (n=100 in both operations) to analyse at 8-hour postoperative intervals which organ functions are impaired (pain, orthostatic function, balance, muscle function, general weakness, psycho-social) that may be responsible for prolonging postoperative stay for more than 24 hours. This study will be hypothesis-generating and in line with the principal investigators' previous approach in an effort to improve fast-track procedures in other surgical specialities.

## **Perspectives**

The scheduled multiple pain treatment and physiology studies will have a major global impact on improving perioperative pain management and on our understanding of the pathogenesis of the observed large inter-individual pain responses to a well-defined major surgical injury. Furthermore, the planned studies with the LIA technique will have major implications for other surgical procedures in which this technique so far has not been applied. Finally, the planned studies will have a major impact on analgesic treatment and functional recovery of hip and knee arthroplasty patients in general.

## **Collaborators**

Professor Finn Cilius Nielsen, Department of Clinical Chemistry, Rigshospitalet, Copenhagen University, Denmark (gene analyses).

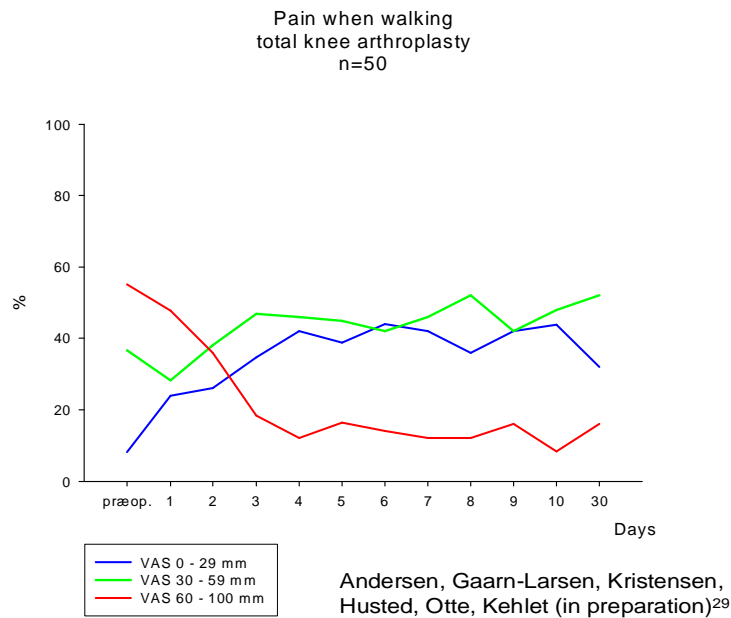


Fig. 1: Pain during walking within the first postoperative month after fast-track knee arthroplasty (n= 50) in patients receiving current best-evidence multimodal analgesia (wound infiltration, COX-2 inhibitor, gabapentin, paracetamol)

### 3.2 Optimising transfusion strategy

#### Liberal vs. restrictive postoperative transfusion triggers in hip arthroplasty

##### Background

Transfusion of red blood cells (RBCs) is indicated when a patient's limit of physiological adaption to progressive normovolaemic anaemia is reached, and this has been reported to occur when the haemoglobin falls below 4.0 mmol/L in healthy individuals and below 5.5 mmol/L in patients with cardiovascular disease.<sup>43,44</sup> Based on these observations, universal transfusion triggers have been developed that recommend administration of RBCs when the haemoglobin level reaches < 4.5 mmol/L in non-cardiac patients and < 6.0 mmol/L in patients with cardiovascular disease.<sup>45,46</sup>

Only one prospective, randomised, controlled clinical trial evaluating a liberal vs. restrictive transfusion strategy has been performed. In that study two groups of critically ill patients were studied, one received RBC transfusion when haemoglobin was < 6.0 mmol/L and the other when it was < 4.5 mmol/L.<sup>47</sup> No overall difference in 30-day survival was found between the two groups. However, patients < 55 years or with an APACHE II score  $\leq$  20 had significantly increased 30-day survival when transfused at the lower transfusion trigger. Subsequently, this landmark study provided the scientific basis for a restrictive transfusion policy aiming at reducing the need for allogenic RBCs in general. In contrast, two, recent, large observational studies reported that mild preoperative anaemia is associated with adverse outcome, including death, in both cardiac<sup>48</sup> and non-cardiac patients.<sup>49</sup> A randomised study, performed by the principal investigators, also showed that low transfusion thresholds may increase morbidity in hip fracture surgery.<sup>50</sup> Finally, our cohort study show that postoperative anaemia (Hb < 6.5 mmol/L) impedes functional mobility after hip fracture surgery,<sup>51</sup> and preliminary

small cohort data suggest that postoperative anaemia may impede quality of life after hip arthroplasty in elderly patients.<sup>52</sup>

On the other hand, administration of RBCs has been associated with morbidity and mortality in both medical and surgical patients.<sup>53</sup> Transfusions are associated with the risk of transmission of infectious agents, postoperative infectious complications, renal dysfunction, multiple organ failure and increased intensive care and hospital stay.<sup>54,55</sup> Administration of RBCs has also been reported to be associated with increased short-term<sup>56</sup> and long-term mortality<sup>57</sup> after coronary by-pass, and recently Koch et al. reported that in patients undergoing cardiac surgery, transfusion of RBC stored for more than 14 days was associated with a significantly increased risk of postoperative complications as well as short- and long-term survival.<sup>58</sup>

### **Study hypothesis**

Hip arthroplasty is associated with a relatively large intraoperative bleeding (average ~ 600 ml)<sup>59</sup> and a postoperative "hidden" blood loss. Consequently, about 30% of patients require blood transfusion (median 2 units/patient).<sup>59</sup> Based upon the above background information, we hypothesise that a liberal transfusion regimen will have a positive effect on functional recovery and quality of life compared with a restricted transfusion regimen. No previous, randomised, large-scale study has hitherto tried to clarify the value of an aggressive vs. a liberal transfusion trigger in patients undergoing hip arthroplasty.<sup>52</sup>

### **Study design**

A randomised clinical trial

Based upon the well-established fast-track set-up at the four research units, the effect of a liberal vs. a restrictive postoperative transfusion therapy on postoperative function will be evaluated.

Sample size: Nine hundred patients (>70 yrs) undergoing hip surgery will be included and randomly allocated to receive postoperative RBC transfusion when haemoglobin levels fall below 6.5 mmol/L (liberal group) or 5.0 mmol/L (restrictive group) to assess the functional mobility and quality of life in the early and late postoperative phases (10% improvement of 6-min walking test 1 week postoperatively,  $p < 0.05$ , power 0.8). Based upon the Cumulated Ambulation Score<sup>60</sup> from own data, a sample size of about 500 patients will be required to demonstrate a 10% improvement.

Endpoints: Validated functional scores from the research group and others (6-min walking test, Cumulated Ambulation Score,<sup>60</sup> Timed Up and Go test,<sup>61</sup> fatigue, the short FACT-anaemia score<sup>62</sup> and the short-form SF-36) will be used, and the incidence of postoperative cognitive dysfunction (POCD) will also be evaluated with established validated techniques.<sup>63</sup> Development of postoperative cardiac morbidity and infectious complications, length of stay in hospital and short (30-day) and long-term (1-year) survival will be recorded along with detailed preoperative assessment of risk factors.

### **Ethical considerations**

In Denmark, as opposed to the rest of the Western world, use of RBC transfusion is steadily increasing, and 73 units of RBCs are transfused per 1,000 inhabitants as compared to 40-45 units of RBCs per 1,000 inhabitants in the rest of Europe, where use of RBC transfusions is decreasing.<sup>59</sup> The Danish transfusion practice therefore offers a unique opportunity to evaluate the effect of a liberal transfusion strategy in elderly patients undergoing surgery, a strategy that in other countries would be considered "unethical" due to unnecessary exposure to blood products in patients who may not need

them. On the other hand, a transfusion trigger for haemoglobin of 6.5 mmol/L is in agreement with current Danish transfusion practice, in which more than 30% of the patients receiving transfusions of RBCs demonstrate a pre-transfusion haemoglobin > 6.0 mmol/L.<sup>51</sup> Therefore, patients included in the present study will not be exposed to a RBC transfusion intensity different from current standard practice. Furthermore, the optimal haemoglobin level for patients > 70 years, i.e. the age group to be included in the present study, remains to be established and underlines the importance of conducting the present study.

### **Perspectives**

The planned study will be unique in several ways. Firstly, because it is the first prospective large, definitive, randomised clinical trial assessing the effect of a liberal vs. restrictive transfusion strategy in elderly, non-critically ill patients with a well-defined fast-track care programme and a focus on functional recovery. Secondly, as mentioned above, the proposed design is only possible to perform in Denmark, due to a more liberal transfusion policy than in the rest of the Western world. Thirdly, the ability to evaluate interventions in a group of patients treated in accordance with the fast-track set-up enables a unique opportunity to evaluate the intervention regarding transfusion therapy in a model with limited confounders. These results may subsequently have unique implications for transfusion strategies in other major operations. Finally, the research group has the documented expertise in fast-track hip and knee arthroplasty, postoperative rehabilitation and transfusion medicine to ensure the performance of the project.

### **Collaborators**

Pär Johansson, Medical Director, Transfusion Service, Rigshospitalet, Copenhagen University and in Capital Region in Denmark.

## **3.3 Optimising postoperative rehabilitation and physiotherapy**

### **Background**

It is well documented that major surgery is followed by a decline in various organ functions<sup>1</sup> including loss of muscle tissue and function, and a reduced cardiovascular adaptive response to exercise that leads to prolonged convalescence with fatigue.<sup>64-66</sup> Subsequently, a rehabilitation phase during both traditional long hospitalisation as well as after discharge has included various programmes for physiotherapy. For this reason and because of concomitant factors with trauma to the limb, intra-hospital and post-discharge physiotherapy has been a key factor in traditional care after hip and knee arthroplasty. The specific role, type and effect of physiotherapy after knee arthroplasty has been questioned in a recent meta-analysis,<sup>67</sup> but the available studies were, however, all done in patients subjected to traditional long hospital stays and late (weeks) initiation of physiotherapy after the operation, thereby allowing further functional deterioration before starting post-discharge intervention. The introduction of fast-track surgery has, especially in colorectal surgery,<sup>3</sup> demonstrated pronounced improvements in physical performance, pulmonary function and body composition about 1 week postoperatively compared with traditional care, that is, at a time when these patients would still have been hospitalised.<sup>68</sup> Hence, improved strength of the quadriceps muscle and handgrip has been demonstrated after fast-track compared with conventional care colonic surgery.<sup>69-71</sup> Conse-

quently, fast-track colonic surgery has led to reduced post-discharge fatigue.<sup>72,73</sup> Thus, physiotherapy during both the short hospitalisation and after discharge has been eliminated (H. Kehlet, unpublished).

There are no data on the indication for or the effect of physiotherapy after discharge in fast-track hip and knee arthroplasty, and where the need may be significantly less compared with traditional care, assuming the same benefits of the fast-track set-up as demonstrated in colonic surgery. A recent survey of the use of post-discharge physiotherapy in Denmark<sup>74</sup> has shown a variable use of physiotherapy, and in mid-Jutland 2 large centres (Aarhus and Holstebro) have no routine use prescribed, providing a unique possibility for performance of the scheduled randomised trials allowing randomisation to +/- physiotherapy.

### **Study hypotheses**

In fast-track hip and knee arthroplasty with discharge to the patient's home 2-3 days postoperatively, a reduced loss of function (range of motion, muscle strength, balance) is expected and assumed to translate into a decreased or no need for post-discharge physiotherapy except for selected patient groups.

### **Study design**

To perform two large randomised studies in hip (n=140) and knee (n= 140) arthroplasty, patients are randomised to either no post-discharge physiotherapy or 12 weeks of traditional physiotherapy.

Endpoint: validated functional scores (joint movement, isometric muscle force, timed up & go (TUG), 6-min walking test, tandem balance test) will be used to assess the intervention 6 and 12 weeks postoperatively.

Sample size: A formal power calculation cannot be performed because there are no data on functional decrease in fast-track hip and knee arthroplasty – but based upon the 6-min walking test data with traditional care,<sup>75</sup> it is estimated that 140 patients in each group will provide sufficient data to detect a significant ( $p < 0.05$ ) treatment effect of at least 10% between groups (power 0.8 and 20% loss of patients during follow-up).

### **Perspectives**

The planned studies will be the first available to assess the need for post-discharge physiotherapy combined with well-established fast-track programmes in hip and knee arthroplasty. In addition, the detailed study will be able to identify specific patient groups which may or may not require physiotherapy. These results will not only be important for these common procedures (about 2,000/1,000,000 inhabitants/yr) but will also be applicable to other major procedures with a fast-track set-up and have major socio-economic implications.

## **3.4 Reducing duration of thromboprophylaxis with preserved safety**

### **Background**

Several randomised trials have documented extended thromboprophylaxis (about 4 weeks vs. 10 days) to be effective and advisable after elective hip arthroplasty (THA) and knee arthroplasty (TKA)<sup>76,77</sup> and major abdominal procedures.<sup>78</sup> These observations and recommendations are based on surgical procedures with traditional care with a postoperative length of stay of around 10 days

which implies a certain degree of non-optimal mobilisation. On the other hand, it has been discussed whether anti-coagulation may increase the risk of infections and other morbidities.<sup>79,80</sup>

Preliminary uncontrolled observations have suggested that early mobilisation may reduce postoperative thromboembolism,<sup>81</sup> which is in accordance with observations with early mobilisation in short-term (~3-4 days) thromboprophylaxis and fast-track THA and TKA with a hospital stay of around 3-4 days (principal investigators, unpublished, including fast-track colonic resection, 2-3 days). Accordingly, expert opinion has suggested that pharmacological thromboembolic prophylaxis may not need to be aggressive or prolonged in patients who are mobilised promptly.<sup>82</sup> Finally, extended thromboembolic prophylaxis may have major socio-economic implications due to direct costs as well as patient compliance and involvement.

So far, no randomised, large-scale study is available to provide information on the optimal duration of thromboembolic prophylaxis in fast-track THA and TKA.

### **Study hypothesis**

Short-term (during hospitalisation) thromboembolic prophylaxis is non-inferior to long-term prophylaxis (30 and 10 days) in fast-track THA and TKA with enforced early mobilisation.

### **Study design**

A large, multi-centre randomised controlled trial in patients undergoing primary unilateral total THA and TKA and receiving prophylaxis with low molecular weight heparin during hospitalisation (~ 3 days) vs. for 30 days after THA and for 10 days after TKA, as recommended internationally.<sup>76,77,83</sup> Patients with a postoperative clinical signs of thromboembolism (swelling of either leg) will undergo compression ultrasound examination and a urine prothrombin fragment 1+2 (uF1+2)<sup>84</sup> to diagnose deep vein thrombosis. All patients are followed for 90 days postoperatively, and all thromboembolic and other vascular complications and/or deaths are registered during this period and treated according to existing recommendations. In addition, a spot urine analysis of uF1+2<sup>84</sup> will be analysed preoperatively and at discharge to characterise the thrombotic potential and to provide final data documentation on this simple diagnostic test.<sup>84</sup>

Primary endpoints: Symptomatic vein thrombosis, pulmonary embolism, myocardial infarction, stroke, and other vascular events. Secondary endpoints: distal deep vein thrombosis.

Sample size: The study is planned as a non-inferiority study. Based on the literature and Danish data, the event rate of all cardiovascular events and venous thrombosis is about 12% (Camilla Rye, PhD Thesis, Copenhagen University, defended March 28, 2008). We consider an absolute risk difference of less than 4% as non-inferiority, and with a power of 80%, a two-sided significant level of 5% will provide a >80% possibility that the upper limit of the 95% confidence interval (CI) for the point estimate is less than 4% for short-term prophylaxis. Consequently, a sample size of 1036 patients will be required in each group, and with an estimated 10% drop-out rate, a total 2280 patients will be included in the study.

### **Ethical considerations**

The duration of thromboembolic prophylaxis after major joint arthroplasties is still debated nationally and internationally regarding the optimal benefit vs. side-effects and costs. In Denmark, the Danish Orthopaedic Society has recommended 7 days of prevention as a compromise, but allowing extended prophylaxis, where considered appropriate (not well-defined). The present study with a shorter dura-

tion of prophylaxis in patients undergoing fast-track early mobilisation/short stay surgery is in accordance with considerations from the highest international expertise.<sup>82</sup> In summary, we consider the study feasible and performable in accordance with good clinical practice and the Declaration of Helsinki.

### **Perspectives**

The present study will be the first of its kind and, hopefully, will document the non-inferiority of short-term thromboembolic prophylaxis in fast-track early mobilisation THA and TKA – operations which have been studied extensively before with various thromboembolic prophylaxis regimens – but with traditional care and hospitalisation of around 10 days.<sup>77</sup> Depending on the results, the study will have major implications for anti-thrombotic regimes in other fast-track, high-risk surgical populations (colorectal surgery, major gynaecological and urological cancer surgery, etc.).

### **Collaborators**

Dr. Michael Rud Lassen, Department of Orthopaedic Surgery, Hørsholm Hospital.

Dr. Lars Carl Borris, Department of Orthopaedic Surgery, Aarhus University Hospital.

## **3.5 Reducing postoperative cognitive dysfunction (POCD)**

### **Background**

One of the well-documented undesirable sequelae after major surgery is a decline in cognitive function (POCD), especially memory.<sup>63,85,86</sup> POCD is a specific entity different from delirium. The incidence of POCD is about 25% within 7-10 days postoperatively with traditional care, declining to about 10-15% 2-3 months after major surgery, including hip and knee arthroplasty.<sup>63,85,86</sup> Old age (>70 yrs) is the most important risk factor.<sup>63,85,86</sup> POCD has a major impact on postoperative recovery and is related to activities of daily living and mortality.<sup>63,85,86</sup> Although the duration of general anaesthesia may correlate with POCD,<sup>63,85,86</sup> use of regional anaesthesia has not reduced the risk of POCD.<sup>87</sup> The pathogenesis of POCD is probably multi-factorial – and presently not clarified. However, there is general agreement about the clinical relevance of POCD, as quoted in a recent editorial: "those involved in the care of elderly patients scheduled to undergo surgery must identify the pathogenic mechanisms and orchestrate appropriate protective and therapeutic interventions to target the pathogenic processes that produce POCD".<sup>88</sup>

Based upon clinical observations by the two principal investigators, POCD after fast-track hip and knee arthroplasty may not appear as commonly as previously observed with traditional care. The underlying mechanisms could be related to the shortened hospital stay per se,<sup>89</sup> with return to daily home activities within 2-3 days at present compared with 7-11 days previously. In addition, the effective non-opioid pain management may be protective, since opioids are well-known to disrupt postoperative sleep architecture,<sup>90,91</sup> and because sleep disturbances may relate to POCD.<sup>92</sup> Furthermore, effective modern non-opioid analgesia may decrease postoperative sleep disturbances (and POCD?) based upon the observation that chronic pain may lead to sleep disturbances.<sup>90</sup> Finally, the inflammatory cytokine response (IL-6) may induce sleep disturbances, fatigue and prolonged convalescence,<sup>29, 93, 94</sup> all of which may predispose to POCD in elderly, susceptible postoperative patients. No study in the literature has hitherto tried to clarify the relative importance of all these

pathogenic mechanisms, and incorporate them into a unifying hypothesis to provide rational strategies for prevention of POCD.

### **Study hypotheses**

Fast-track surgery combined with a non-opioid set-up will decrease POCD after hip and knee arthroplasty compared with traditional care.

### **Study design**

Based on the established fast-track set-up at the 2 centres with a hospital stay of about 2-3 days together with non-opioid effective analgesia,<sup>16,21,22</sup> which is continued after discharge (see pain section), our aim is to assess in detail the incidence of POCD with established validated techniques,<sup>95</sup> and compare this incidence with that seen after traditional care.<sup>63,86</sup> In a subset of patients, modification of the inflammatory response by perioperative glucocorticoid treatment (see pain section) will be studied in a randomised study, and sleep architecture will be assessed in a subset of the study. In the total study, the inflammatory response markers (IL-6), pain, and sleep quality (questionnaires) will be correlated with POCD.

Sample size: Based upon the research group's previous experiences,<sup>63,85,87</sup> the hypothesis is that the fast-track, non-opioid set-up will decrease POCD to 5% after hip and knee arthroplasty (as observed in outpatient minor surgery<sup>89</sup>), whereas previously POCD was about 10-15%.<sup>63,85,86</sup> Thus, 400 patients undergoing fast-track surgery compared with 250 undergoing traditional care will provide a statistical power of 85% to allow a detection of the assumed difference (5% vs. about 12%) at the 5% significance level, assuming that late postoperative follow-up examination may not be possible in 10-15% of patients.

### **Perspectives**

The planned study will be unique and for the first time include several POCD pathogenic mechanisms not previously reported.<sup>88</sup> The data set will also allow analyses of the relationship between POCD and possible pathogenic mechanisms (pain, sleep quality, inflammatory responses) which have not been studied before in large patient groups and with fast-track set-up. The results are assumed to have widespread perspectives when translated to other major procedures.<sup>88</sup> The research group has documented expertise in POCD and fast-track hip and knee arthroplasty to ensure optimal performance of the project.

### **Collaborators**

Dr. Lars Rasmussen, Dept. Anaesthesia, Rigshospitalet, Copenhagen University.

## **3.6 Fast-track, one-stage revision surgery for infected hip arthroplasty**

### **Background**

Chronic infection in total hip arthroplasty is a feared and severe complication. It occurs in about 1-2% of all primary total hip arthroplasty,<sup>96</sup> and has the potential to ruin all the advantages provided by the primary total hip arthroplasty. The infection threatens the function of the joint, preservation of the limb, and occasionally the life of the patient. The treatment is difficult and prolonged, often with poor outcome, and the patient may become a permanent invalid. Approximately 150 Danish patients each year undergo revision surgery due to deep infection in a total hip arthroplasty.<sup>96</sup>

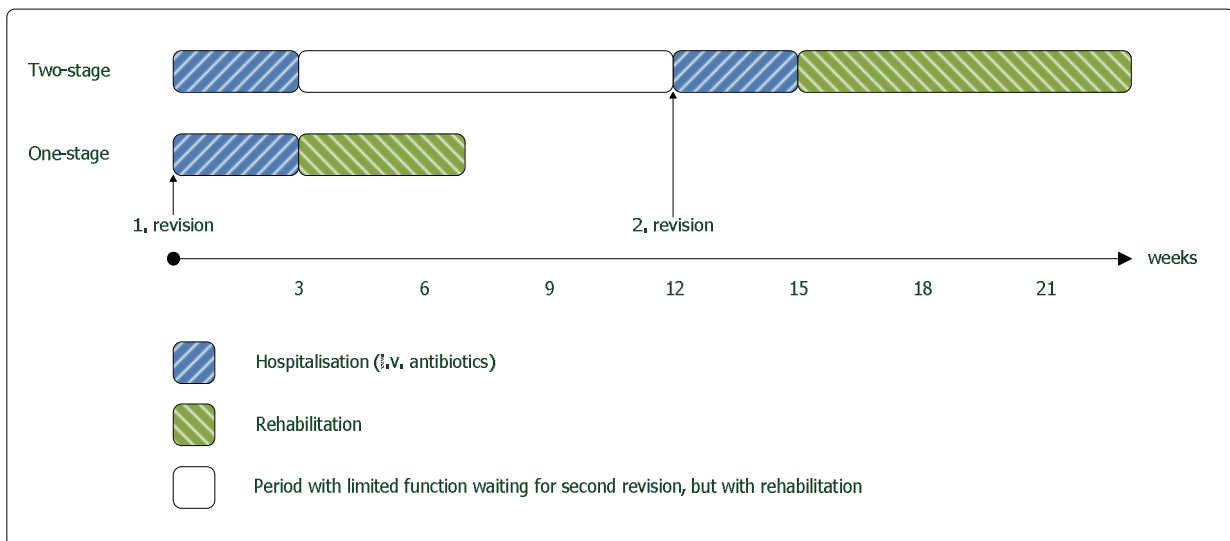


Two-stage revision (see figure below)

Currently, the gold standard for chronic infection in THAs is major revision surgery, consisting of a “two-stage” procedure<sup>97,98</sup> with primary evacuation of implants, removal of cement and soft tissues, extensive irrigation, and insertion of a temporary antibiotic-loaded cement spacer.<sup>98</sup> However, the inserted spacer allows the patient only limited function. The patient is hospitalised for 3 weeks and receives systemic antibiotics.<sup>98</sup> At a second surgical procedure about 3-6 months later, a new revision THA is inserted followed by a rehabilitation period of several weeks.

One-stage revision (see figure below)

Another and less well established procedure is “one-stage” revision, in which evacuation of implants and insertion of new implants are carried out in one procedure. This procedure has the considerable potential to shorten total hospitalisation time, patients immobilisation, and rehabilitation, increase quality of life and reduce costs.<sup>99,100</sup> However, only very small-scale data are available,<sup>99,100</sup> and these are not combined with a fast-track set-up, including final rehabilitation.

**Study hypothesis**

One-stage revision surgery can be performed with substantial benefits for the patients in terms of the total hospitalisation period and faster rehabilitation (see figure above), and it can especially eliminate the 3- to 6-month period of severe functional disability between the two-stage revisions, with its assumed deleterious consequences for final rehabilitation.

**Study design**

A non-randomised, consecutive, hypothesis-generating cohort study (N=100). Data will be compared with data from the two-stage procedure in Denmark<sup>96</sup> and the literature available. Inclusion and treatment of patients will be conducted in the two orthopaedic centres (Aarhus and Hvidovre University Hospitals). The data will be analysed in detail regarding functional recovery (see physiotherapy section) as well as assessments of economic implications. Perioperative care principles will be as in fast-track primary hip arthroplasty.

## **Perspectives**

If one-stage revision can be shown to result in reduced total hospitalisation time and faster rehabilitation and with a low number of re-infections, the study will support this approach as being the treatment of choice.

### **3.7 Safety aspects in fast-track surgery**

#### **Risk of hip dislocation and implant loosening**

##### **Background**

Early mobilisation and weight bearing have been debated as risk factors in fast-track hip arthroplasty. Whereas satisfactory post-operative treatment of pain in combination with early mobilisation may provide protection against cognitive dysfunction and thromboembolic complications, it may also cause patients to increase strain on the newly operated limb leading to potential adverse effects on long-term implant performance or survival.

##### Dislocation

The most common surgical complication in THA is dislocation of the hip, which may occur in 2-5% of patients, or more frequently in the obese.<sup>101</sup> Opponents of fast-track surgery have suggested that dislocation increases with short hospital stays.<sup>102</sup> A preliminary, small-scale (N=265) randomised study did not support the notion that removal of functional restrictions increases early dislocation,<sup>103</sup> but this study focused on specific movements and not on the influence of duration of hospitalisation per se.

Thus, there is no valid information on the potential risk for dislocation with decreased length of hospitalisation in fast-track hip arthroplasty.

##### Implant loosening

Survival of joint prostheses, in terms of the time from insertion of the first implant until reoperation, is a major concern both for the patient and the National Health Service. The risk of loosening depends on age and function of the patient and occurs in about 10-15% after 10-15 years.<sup>104</sup> The stability of uncemented arthroplasty depends on the primary surgical fixation until secondary fixation by bony anchorage has been established. Overloading a newly inserted uncemented implant may potentially cause mechanical loosening, and clinical studies have shown that early migration of implants is related to premature revision surgery.<sup>105</sup> Implant micromotion is therefore a surrogate indicator of implant survival and can be measured by roentgen stereophotogrammetric analysis (RSA)<sup>106,107</sup> in clinical trials.<sup>105,108-110</sup> As RSA provides a very precise measurement of implant migration with a precision of < 0.1 mm,<sup>108,109</sup> a short follow-up of 2-5 years is sufficient to predict the long-term performance of knee and hip prostheses.<sup>105,110</sup>

No studies are available on the risk of implant loosening in fast-track hip arthroplasty. The fast-track centres are therefore provided with a unique opportunity to evaluate the risk of implant loosening compared with traditional care evaluated with RSA.

##### **Study hypotheses**

1. Fast-track surgery does not increase the risk of hip dislocation.
2. Fast-track surgery does not jeopardize implant stability.

## **Study design**

### Dislocation

This project will include a follow-up of a consecutive group of about 7,000 THA patients from the fast-track collaborative centres, and results will be compared with results from the Danish Hip Register and the National Hospital Registries as well as with previously published data and data from non fast-track centres.

### Implant stability

A prospective cohort of fast-track THA patients with cementless Bimetric implants will be monitored with RSA and compared with a group of patients subjected to traditional care (historic controls from own centres).

Sample size: the study is planned to be a non-inferiority study. From the literature the rate of implant migration of more than 1-2 mm is 25%.<sup>111</sup> An absolute risk difference of less than 5% will call for non-inferiority. If the rate of implant migration of more than 1 mm in fast-track patients is 0.18 then with a the power of 80% and a two-sided significance level of 5% (i.e that the upper limit of the 95% confidence interval (CI) around the point estimate for migration > 1 mm in the fast-track group will be less than 30% with a 80% possibility) we need a sample size of 104 fast-track patients. About 10% of the patients will not fulfil the study and therefore 120 patients will be included in cohort. Parameters: implant stability based on RSA.

## **Perspectives**

These studies provide safety data to be compared with the otherwise well documented advantages of fast-track hip arthroplasty in order to facilitate general implementation of the concept.

## **Patient satisfaction and quality of life**

### **Background**

Although fast-track surgery is well-documented to improve recovery, decrease organ dysfunctions, need for hospitalisation and convalescence,<sup>1,3</sup> a potential side-effect of early discharge may be decreased patient satisfaction, uncertainty, and decreased quality of life with risk of early readmissions. Although intensified preoperative patient information and information during hospitalisation are key factors in fast-track surgery, less attention has been paid to post-discharge patient information.

In cooperation with the Centre of Pervasive Healthcare University of Aarhus, Denmark, we have developed an interactive Mobile HomeCare (MOHOC) device in order to perform Remote Rehabilitation Support (RRS) (manuscript in preparation). The concept includes film clips, 3D animation, verbal and written information and videophone communication, all available as wireless technology, thereby supporting the patient physically and psychologically in a new and easy way. Furthermore, the equipment provides unique possibilities for interactive data collection.

### **Hypothesis**

The RRS system will improve quality of life and physical function compared with conventional set-up of fast-track hip arthroplasty.

## **Study design**

A randomised, controlled trial to compare quality of life and physical function in fast-track hip arthroplasty. Outcome parameters are quality of life, anxiety, pain, and physical function (see physiotherapy section).

**Sample size:** The sample size is based on our own quality of life study.<sup>112</sup> The risk of a type 1 error is set at 5%, using a two-sided analysis, and the power at 80%. Quality of life is expected to be 0.85 (SD 0.15) in the control group, and 0.95 (SD 0.15) in the intervention group leading to at least 63 patients in each group. To account for a potential drop-out, 140 patients will be included.

## **Perspectives**

The RRS system may provide a unique possibility to create a homecare environment to observe, support and intervene with the patient, including assessment of complaints and degree of activities. Thus the study supports other tele-medicine activities, but where no information is available within fast-track surgery and the present results may therefore have widespread implications within all surgical specialities.

## **4 Organisation**

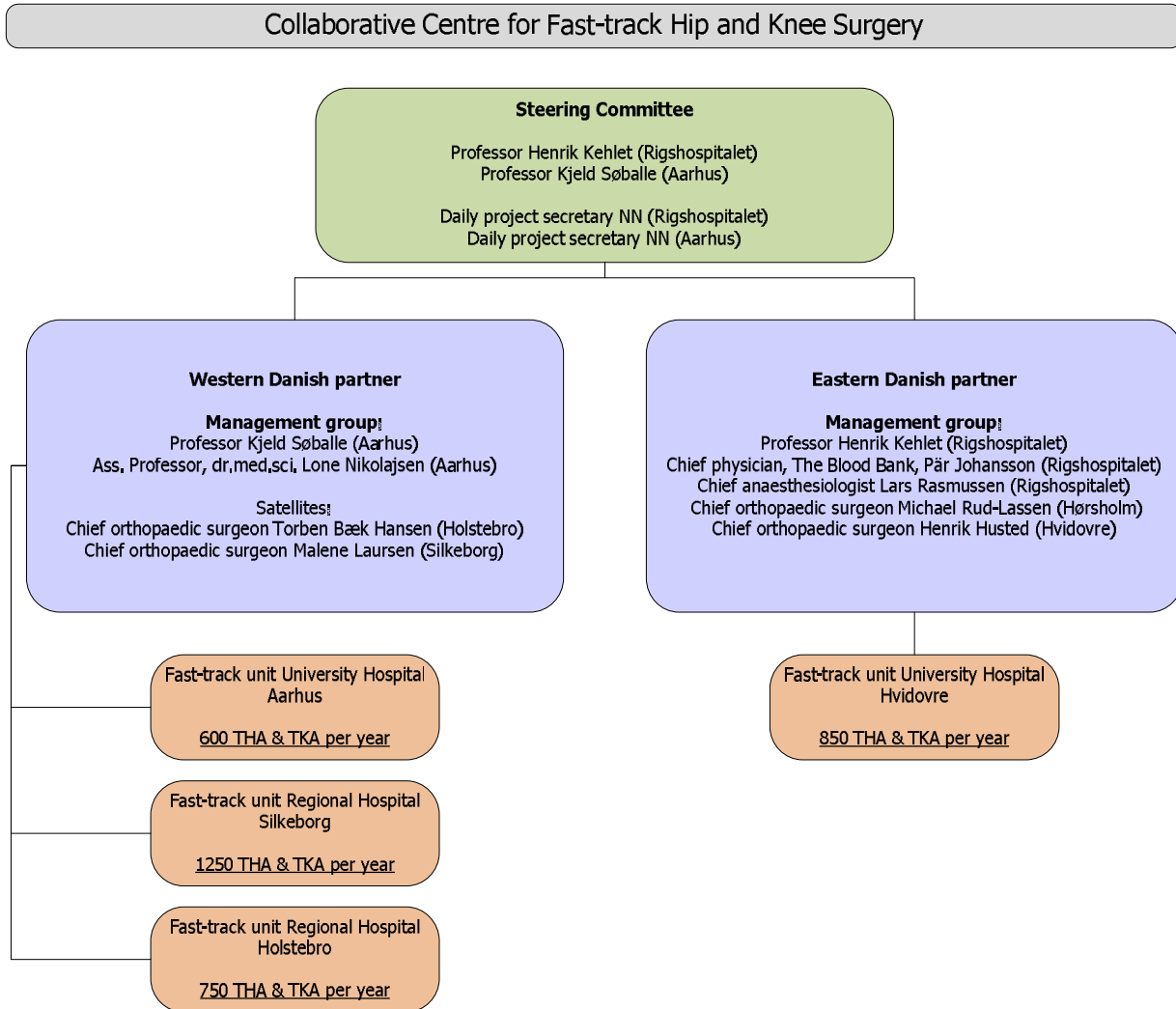
### **Management**

The overall coordination of the centre will be ensured by the Steering Committee. The Centre leadership will be shared between the two principal investigators, Professor Henrik Kehlet and Professor Kjeld Søballe. This is the most suitable way to manage the project because they are locally employed in the Eastern and Western Danish Partner groups, respectively. Henrik Kehlet is currently Professor of Perioperative Therapy at Copenhagen University Hospital, which allows >90% time for research. The current project will take 50% of Henrik Kehlets research time, the remaining part being allocated to fast-track surgery in other surgical specialities as well as a main research project "Transition from acute to persistent postsurgical pain". Kjeld Søballe is currently professor of orthopaedics at Aarhus University Hospital with 50% time for research and education and 50% time for surgery. The surgical part will be reduced 35% and time spent on education will be reduced to 1-2 hours a week, thus giving 50% time to focus on the Centre for Fast-track Hip and Knee Surgery.

Two project secretaries will be employed by the project, one by the Eastern and one by the Western Danish partner groups, with responsibility for the day-to-day management of the Centre and to ensure a swift and competent exchange of information between the many project partners and other relevant stakeholders. The Steering Committee handles the overall research and financial oversight and will meet every third month and whenever it is required for the proper implementation of its responsibilities.

The Centre for Fast-track Hip and Knee Surgery will be organised in two groups based on geographical location. The Western Danish Partner consists of the Orthopaedic Research and Fast-track Unit at Aarhus University Hospital, the Fast-track Unit at Regional Hospital Silkeborg and the Fast-track Unit at Regional Hospital Holstebro, and The Eastern Danish Partner consists of the Orthopaedic Fast-track and Anaesthesia Research Unit at Hvidovre University Hospital. These partners represent a fourth of all THAs/TKAs performed in Denmark with a total of about 3500 operations per year, which

provide a unique possibility for a new and thorough research within the fast-track surgery area based on an interdisciplinary and novel approach. The management groups are, together with the Steering Committee, responsible for supervision of research conduct and quality in the groups and will meet once a month. The management group includes documented expertise within the specific areas of pain, cognitive dysfunction, thromboembolism, and transfusion policy.



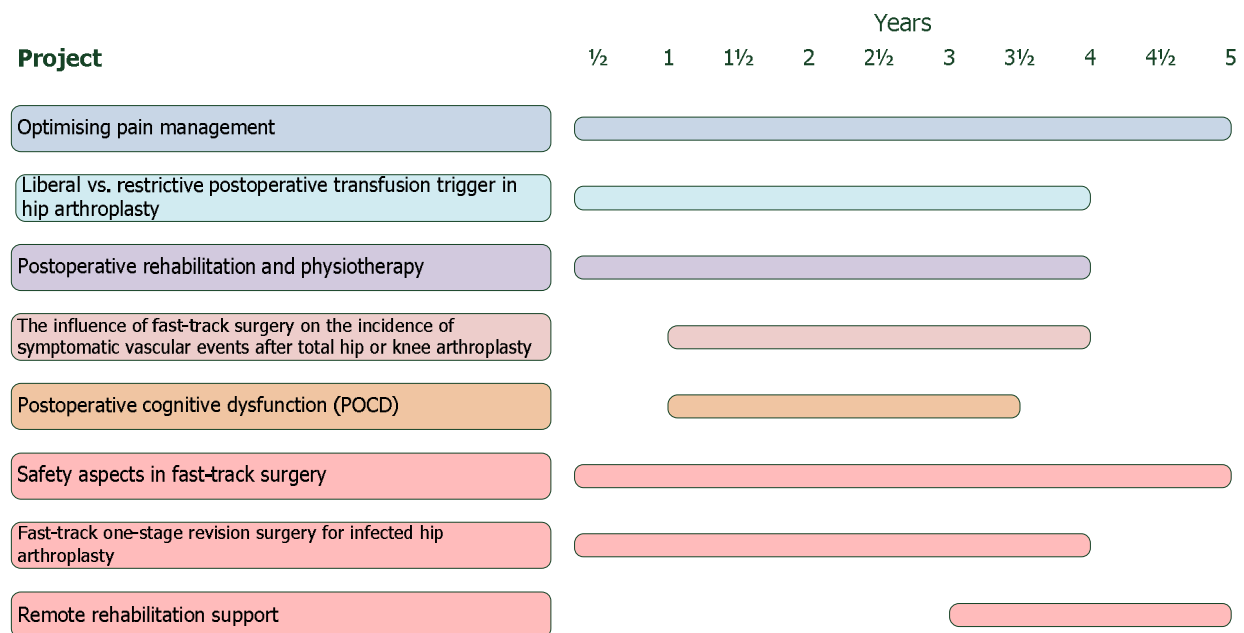
PhD students and BMedSc graduates are expected to join the centre and will be supervised on a daily basis by postdoctoral fellows, senior research personnel and the two principal investigators. The scientific communication will, apart from email correspondence, be facilitated by creating a website containing both a password protected and a public area. The Centre website will be created, managed and updated by a webmaster. The Centre database will be created, maintained and expanded by the Steering Committee.

Seminars will be held once or twice a year hosted by each partner at least three times to ensure a continuous exchange of information regarding the project and its scientific progress.

### International collaboration

Both principal investigators have documented up-to-date research into the various projects, and with current adjustments based upon ongoing discussions with leading international centres within the specific topics. No specific international collaboration has been established because the research project is considered to be unique because of the already established national fast-track centres, the unique possibilities to do clinical research in Denmark with complete postoperative follow-up and the documented frontline international expertise available within the project group. The proposed projects cannot be performed on an international basis due to different organisations, health care systems, follow-up possibilities, etc., all of which are available and optimal in the Danish centres alone.

## 5 Research project schedule



Some of the projects will continue beyond the 5 years because the Centre for Fast-track Hip and Knee Surgery is expected to be well established and maintained at that time. Also future projects undoubtedly will be performed based upon the achieved results.

## 6 Funding

Formation of the collaboration is dependent on both intramural and extramural funding. Aarhus University Hospital, Hvidovre Hospital, Holstebro Hospital and Rigshospitalet are strongly supportive for the initiative and will provide the necessary space and basic equipment needed to conduct the projects (see enclosures). Moreover, basic running expenses will be allocated to the surgical departments. In addition, various levels of basic expenditures are covered by the centres, including implants and medical treatments. Finally, we expect that each geographical management group will continue to raise additional funding from external sources.

As described in the enclosed budget (appendix 3), the applied resources from the Lundbeck Foundation are intended to cover all the essential initial costs for salaries for VIPs, technicians, new equipment, project coordination and project-related expenses, such as additional diagnostic evaluations, biochemical analyses and medical treatment. As requested, a reduced budget is enclosed (appendix 4), and the applied resources are cut back by salaries for two VIPs (PhD students) because there is a great demand for technicians to govern the projects on postoperative cognitive dysfunction, rehabilitation and physiotherapy, thromboprophylaxis and the pain studies. Furthermore, the cost for apparatus has been removed because the study requiring expenses for a navigation system has been eliminated. Financing from various national sources will be sought to raise one-third or two-thirds of the costs of the PhD projects, whereby the number of PhD students employed may be 2-3 times as high.

We expect that results obtained after 5 years of research on fast-track surgery in Hip and Knee Arthroplasty will be scientifically documented and will justify general implementation both nationally and internationally. However, further research regarding remaining problems will be continued in the Centre, exceeding the 5 years of financial support from the Lundbeck Foundation.

## **7 Framework for research, education and recruitment**

The collaborative centre will be highly integrated with the PhD education at The University of Aarhus and The University of Copenhagen, and we will be able to provide all the necessary supervision for students or "clinical assistants" from the clinical departments as well as medical students enrolled in the Graduate School of Health Sciences' "Research Year" programme. The expected number of PhD students directly financed and co-financed by the Centre is expected to be around 10, in addition to these there will be affiliated PhDs working in related areas. The PhD students will be recruited from among both foreign and Danish candidates to ensure an international dimension of the project.

The Steering Committee has many years' experience in collaborating with clinical departments and research laboratories, national as well as international and supervising PhDs and publishing medical theses.

In the context of education, we feel that the establishment of the described formal collaboration is important by providing a rich environment, in which MDs and PhDs from different clinical entities come in close contact with key scientific personnel. Successful optimisation of an entire surgical course requires a close multi-disciplinary collaboration between all involved personnel, and including sufficient follow-up after discharge. The present project is unique in that it covers all these aspects.

A list of 10 tentative publications (with tentative journals) from the project are listed below, representing the different focus areas of the Centre for Fast-track Hip and Knee Surgery:

1. Optimisation of the high-volume, local anaesthetic infiltration technique (LIA) > 4 studies + 1 major study vs. "gold standard" (continuous peripheral nerve block). Journals: Anesthesiology, J Bone Joint Surg (Am).

2. Effect of perioperative glucocorticoid on postoperative pain and rehabilitation. 1 short-term randomised study + 1 subsequent large (n = > 400) multi-centre randomised study on safety and functional recovery. Journals: Anesthesiology, J Bone Joint Surg (Am)., potentially Lancet / JAMA
3. Optimising post-discharge pain after hip and knee arthroplasty. Journals: Anesthesiology, J Bone Joint Surg (Am).
4. Early and late postoperative cognitive dysfunction after fast-track hip and knee arthroplasty. Journal: Anesthesiology, Lancet
5. Liberal vs. restrictive transfusion strategy in hip and knee arthroplasty – effects on postoperative rehabilitation. Journals: Lancet, JAMA / N Engl J Med
6. The need for post-discharge physiotherapy after fast-track hip and knee arthroplasty. Journal: Br J Med
7. Short-term vs. long-term thromboembolic prophylaxis in fast-track hip and knee arthroplasty. A large randomised study. Journal: N Engl J Med
8. Is fast-track hip and knee arthroplasty safe in terms of dislocation or implant loosening? Journal: J Bone Joint Surg (Am).
9. Improving patient satisfaction and rehabilitation – the remote rehabilitation support system (RRS). Journal: Br J Med
10. Fast-track, one-stage revision surgery for infected hip arthroplasty. Journal: J Bone Joint Surg (Am)

## **8 Perspectives and implications of the research programme**

The planned research programme will have major implications for patient comfort by reducing pain and morbidity as well as having major socio-economic consequences by delineating a rational approach for postoperative physiotherapy, thromboembolic prophylaxis, and cognitive dysfunction. The centres have a unique potential to perform the research with a volume of >3000 arthroplastic operations annually. The research programme is independent of the pharmaceutical industry because the pain studies include well-known un-patented drugs, but now applied in a new, multimodal set-up, and the studies in thromboembolism are in opposition to the current research and recommendations, which have been supported by the pharmaceutical industry. The full research programme, therefore, is an example of the combined need for major research support for clinical interventions not otherwise obtainable from usual sources.

The perspectives go far beyond the two surgical procedures addressed because the results may be applicable to other orthopaedic procedures as well as major procedures in other surgical specialities

1-3.



## 9 Reference list

1. Kehlet H, Dahl JB. Anaesthesia, surgery, and challenges in postoperative recovery. *Lancet* 2003; 362(9399):1921-1928.
2. Kehlet H, Wilmore DW. Evidence-based surgical care and the evolution of fast-track surgery. *Ann Surg.* In press.
3. Kehlet H. Fast-track colorectal surgery. *Lancet* 2008; 371(9615):791-793.
4. Husted H, Hansen HC, Holm G et al. [Length of stay in total hip and knee arthroplasty in Denmark I: volume, morbidity, mortality and resource utilization. A national survey in orthopaedic departments in Denmark]. *Ugeskr Laeger* 2006; 168(22):2139-2143.
5. Moiniche S, Hansen BL, Christensen SE, Dahl JB, Kehlet H. [Patients' activity and length of stay after hip arthroplasty with balanced analgesia and early mobilization]. *Ugeskr Laeger* 1992; 154(21):1495-1499.
6. Husted H, Holm G, Jacobsen S. Predictors of length of stay and patient satisfaction after hip and knee replacement surgery. Fast-track experience in 712 patients. *Acta Orthop.* In press.
7. Holte K, Kristensen BB, Valentiner L, Foss NB, Husted H, Kehlet H. Liberal versus restrictive fluid management in knee arthroplasty: a randomized, double-blind study. *Anesth Analg* 2007; 105(2):465-474.
8. Kehlet H, Dahl JB. The value of "multimodal" or "balanced analgesia" in postoperative pain treatment. *Anesth Analg* 1993; 77(5):1048-1056.
9. Kehlet H. Postoperative opioid sparing to hasten recovery: what are the issues? *Anesthesiology* 2005; 102(6):1083-1085.
10. PROSPECT Procedure-specific postoperative pain management. Available from: [www.postoppain.org](http://www.postoppain.org). 2007.
11. Kehlet H, Wilkinson RC, Fischer HB, Camu F. PROSPECT: evidence-based, procedure-specific postoperative pain management. *Best Pract Res Clin Anaesthesiol* 2007; 21(1):149-159.
12. Werner MU, Duun P, Kehlet H. Prediction of postoperative pain by preoperative nociceptive responses to heat stimulation. *Anesthesiology* 2004; 100(1):115-119.
13. Iffeld BM, Le LT, Meyer RS et al. Ambulatory continuous femoral nerve blocks decrease time to discharge readiness after tricompartiment total knee arthroplasty: a randomized, triple-masked, placebo-controlled study. *Anesthesiology* 2008; 108(4):703-713.
14. Andersen KV, Pfeiffer-Jensen M, Haraldsted V, Soballe K. Reduced hospital stay and narcotic consumption, and improved mobilization with local and intraarticular infiltration after hip arthroplasty: a randomized clinical trial of an intraarticular technique versus epidural infusion in 80 patients. *Acta Orthop* 2007; 78(2):180-186.
15. Andersen LJ, Poulsen T, Krogh B, Nielsen T. Postoperative analgesia in total hip arthroplasty: a randomized double-blinded, placebo-controlled study on preoperative and postoperative ropivacaine, ketorolac, and adrenaline wound infiltration. *Acta Orthop* 2007; 78(2):187-192.
16. Andersen LØ, Husted H, Otte K.S., Kristensen BB, Kehlet H. High-volumen infiltration analgesia in total knee arthroplasty. A randomized, double-blind, placebo-controlled trial. (submitted). *Br J Anaesth* 2008.

17. Andersen LØ, Kristensen BB, Husted H, Otte K.S., Gaarn-Larsen L., Kehlet H. Local anesthetics after total knee arthroplasty: intra- vs. extraarticular administration? A randomised, double-blind, placebo-controlled study. *Acta Orthop*. In press.
18. Andersen LØ, Husted H, Otte K.S., Kristensen BB, Kehlet H. A compression bandage prolongs duration of local infiltration analgesia in total knee arthroplasty. *Acta Orthop*. In press.
19. Busch CA, Shore BJ, Bhandari R et al. Efficacy of periarticular multimodal drug injection in total knee arthroplasty. A randomized trial. *J Bone Joint Surg Am* 2006; 88(5):959-963.
20. Reilly KA, Beard DJ, Barker KL, Dodd CA, Price AJ, Murray DW. Efficacy of an accelerated recovery protocol for Oxford unicompartmental knee arthroplasty--a randomised controlled trial. *Knee* 2005; 12(5):351-357.
21. Rostlund T, Kehlet H. High-dose local infiltration analgesia after hip and knee replacement--what is it, why does it work, and what are the future challenges? *Acta Orthop* 2007; 78(2):159-161.
22. Toftdahl K, Nikolajsen L, Haraldsted V, Madsen F, Tonnesen EK, Soballe K. Comparison of peri- and intraarticular analgesia with femoral nerve block after total knee arthroplasty: a randomized clinical trial. *Acta Orthop* 2007; 78(2):172-179.
23. Vendittoli PA, Makinen P, Drolet P et al. A multimodal analgesia protocol for total knee arthroplasty. A randomized, controlled study. *J Bone Joint Surg Am* 2006; 88(2):282-289.
24. Fowler SJ, Symons J, Sabato S, Myles PS. Epidural analgesia compared with peripheral nerve blockade after major knee surgery: a systematic review and meta-analysis of randomized trials. *Br J Anaesth* 2008; 100(2):154-164.
25. Diatchenko L, Nackley AG, Slade GD et al. Catechol-O-methyltransferase gene polymorphisms are associated with multiple pain-evoking stimuli. *Pain* 2006; 125(3):216-224.
26. Diatchenko L, Nackley AG, Tchivileva IE, Shabalina SA, Maixner W. Genetic architecture of human pain perception. *Trends Genet* 2007; 23(12):605-613.
27. Tegeder I, Costigan M, Griffin RS et al. GTP cyclohydrolase and tetrahydrobiopterin regulate pain sensitivity and persistence. *Nat Med* 2006; 12(11):1269-1277.
28. De Jongh RF, Vissers KC, Meert TF, Booij LH, De Deyne CS, Heylen RJ. The role of interleukin-6 in nociception and pain. *Anesth Analg* 2003; 96(4):1096-103, table.
29. Hall GM, Peerbhoy D, Shenkin A, Parker CJ, Salmon P. Relationship of the functional recovery after hip arthroplasty to the neuroendocrine and inflammatory responses. *Br J Anaesth* 2001; 87(4):537-542.
30. Ackland GL, Scollay JM, Parks RW, de B, I, Mythen MG. Pre-operative high sensitivity C-reactive protein and postoperative outcome in patients undergoing elective orthopaedic surgery. *Anaesthesia* 2007; 62(9):888-894.
31. Podgoreanu MV, White WD, Morris RW et al. Inflammatory Gene Polymorphisms and Risk of Postoperative Myocardial Infarction After Cardiac Surgery. *Circulation* 2006; 114(1\_suppl):I-275.
32. Kardash KJ, Sarrazin F, Tessler MJ, Velly AM. Single-dose dexamethasone reduces dynamic pain after total hip arthroplasty. *Anesth Analg* 2008; 106(4):1253-7, table.
33. Kehlet H. Glucocorticoids for peri-operative analgesia: how far are we from general recommendations? *Acta Anaesthesiol Scand* 2007; 51(9):1133-1135.
34. Romundstad L, Stubhaug A. Glucocorticoids for acute and persistent postoperative neuropathic pain: what is the evidence? *Anesthesiology* 2007; 107(3):371-373.

35. Andersen LØ, Gaarn-Larsen L., Kristensen B, Husted H, Otte K.S., Kehlet H. 4 weeks post-discharge pain patterns after fast-track hip and knee arthroplasty. (to be submitted in May 2008). 2008.
36. Kehlet H, Jensen TS, Woolf CJ. Persistent postsurgical pain: risk factors and prevention. *Lancet* 2006; 367(9522):1618-1625.
37. Nikolajsen L, Brandsborg B, Lucht U, Jensen TS, Kehlet H. Chronic pain following total hip arthroplasty: a nationwide questionnaire study. *Acta Anaesthesiol Scand* 2006; 50(4):495-500.
38. Mogensen T, Simonsen L, Scott NB, Henriksen JH, Kehlet H. Tachyphylaxis associated with repeated epidural injections of lidocaine is not related to changes in distribution or the rate of elimination from the epidural space. *Anesth Analg* 1989; 69(2):180-184.
39. Romundstad L, Breivik H, Niemi G, Helle A, Stubhaug A. Methylprednisolone intravenously 1 day after surgery has sustained analgesic and opioid-sparing effects. *Acta Anaesthesiol Scand* 2004; 48(10):1223-1231.
40. Mira JP, Cariou A, Grall F et al. Association of TNF2, a TNF-alpha promoter polymorphism, with septic shock susceptibility and mortality: a multicenter study. *JAMA* 1999; 282(6):561-568.
41. Reid CL, Perrey C, Pravica V, Hutchinson IV, Campbell IT. Genetic variation in proinflammatory and anti-inflammatory cytokine production in multiple organ dysfunction syndrome. *Crit Care Med* 2002; 30(10):2216-2221.
42. Jones KG, Brull DJ, Brown LC et al. Interleukin-6 (IL-6) and the prognosis of abdominal aortic aneurysms. *Circulation* 2001; 103(18):2260-2265.
43. Carson JL, Duff A, Poses RM et al. Effect of anaemia and cardiovascular disease on surgical mortality and morbidity. *Lancet* 1996; 348(9034):1055-1060.
44. Madjdpour C, Spahn DR, Weiskopf RB. Anemia and perioperative red blood cell transfusion: a matter of tolerance. *Crit Care Med* 2006; 34(5 Suppl):S102-S108.
45. Practice guidelines for perioperative blood transfusion and adjuvant therapies: an updated report by the American Society of Anesthesiologists Task Force on Perioperative Blood Transfusion and Adjuvant Therapies. *Anesthesiology* 2006; 105(1):198-208.
46. Stainsby D, MacLennan S, Thomas D, Isaac J, Hamilton PJ. Guidelines on the management of massive blood loss. *Br J Haematol* 2006; 135(5):634-641.
47. Hebert PC, Wells G, Blajchman MA et al. A multicenter, randomized, controlled clinical trial of transfusion requirements in critical care. Transfusion Requirements in Critical Care Investigators, Canadian Critical Care Trials Group. *N Engl J Med* 1999; 340(6):409-417.
48. Karkouti K, Wijeyesundera DN, Beattie WS. Risk associated with preoperative anemia in cardiac surgery: a multicenter cohort study. *Circulation* 2008; 117(4):478-484.
49. Wu WC, Schiffner TL, Henderson WG et al. Preoperative hematocrit levels and postoperative outcomes in older patients undergoing noncardiac surgery. *JAMA* 2007; 297(22):2481-2488.
50. Foss NB, Kristensen MT, Jensen PS, Palm H, Krashennikoff M, Kehlet H. The effects of liberal vs. restrictive transfusion thresholds on ambulation and outcome after hip fracture surgery (submitted). *Transfusion* 2008.
51. Foss NB, Kristensen MT, Kehlet H. Anaemia impedes functional mobility after hip fracture surgery. *Age Ageing* 2008; 37(2):173-178.

52. Conlon NP, Bale EP, Herbison GP, McCarroll M. Postoperative anemia and quality of life after primary hip arthroplasty in patients over 65 years old. *Anesth Analg* 2008; 106(4):1056-61, table.
53. Koch CG, Li L, Duncan AI et al. Morbidity and mortality risk associated with red blood cell and blood-component transfusion in isolated coronary artery bypass grafting. *Crit Care Med* 2006; 34(6):1608-1616.
54. Moore FA, Moore EE, Sauaia A. Blood transfusion. An independent risk factor for postinjury multiple organ failure. *Arch Surg* 1997; 132(6):620-624.
55. Vincent JL, Baron JF, Reinhart K et al. Anemia and blood transfusion in critically ill patients. *JAMA* 2002; 288(12):1499-1507.
56. Michalopoulos A, Tzelepis G, Dafni U, Geroulanos S. Determinants of hospital mortality after coronary artery bypass grafting. *Chest* 1999; 115(6):1598-1603.
57. Engoren MC, Habib RH, Zacharias A, Schwann TA, Riordan CJ, Durham SJ. Effect of blood transfusion on long-term survival after cardiac operation. *Ann Thorac Surg* 2002; 74(4):1180-1186.
58. Koch CG, Li L, Sessler DI et al. Duration of red-cell storage and complications after cardiac surgery. *N Engl J Med* 2008; 358(12):1229-1239.
59. Danish Transfusion Data Base Report. 2005.
60. Foss NB, Kristensen MT, Kehlet H. Prediction of postoperative morbidity, mortality and rehabilitation in hip fracture patients: the cumulated ambulation score. *Clin Rehabil* 2006; 20(8):701-708.
61. Kristensen MT, Foss NB, Kehlet H. Timed "up & go" test as a predictor of falls within 6 months after hip fracture surgery. *Phys Ther* 2007; 87(1):24-30.
62. Cella D. The Functional Assessment of Cancer Therapy-Anemia (FACT-An) Scale: a new tool for the assessment of outcomes in cancer anemia and fatigue. *Semin Hematol* 1997; 34(3 Suppl 2):13-19.
63. Moller JT, Cluitmans P, Rasmussen LS et al. Long-term postoperative cognitive dysfunction in the elderly ISPOCD1 study. ISPOCD investigators. International Study of Post-Operative Cognitive Dysfunction. *Lancet* 1998; 351(9106):857-861.
64. Christensen T, Kehlet H. Postoperative fatigue. *World J Surg* 1993; 17(2):220-225.
65. Hall GM, Salmon P. Physiological and psychological influences on postoperative fatigue. *Anesth Analg* 2002; 95(5):1446-50, table.
66. Rubin GJ, Hotopf M. Systematic review and meta-analysis of interventions for postoperative fatigue. *Br J Surg* 2002; 89(8):971-984.
67. Minns Lowe CJ, Barker KL, Dewey M, Sackley CM. Effectiveness of physiotherapy exercise after knee arthroplasty for osteoarthritis: systematic review and meta-analysis of randomised controlled trials. *BMJ* 2007; 335(7624):812.
68. Basse L, Raskov HH, Hjort JD et al. Accelerated postoperative recovery programme after colonic resection improves physical performance, pulmonary function and body composition. *Br J Surg* 2002; 89(4):446-453.
69. Gatt M, Anderson AD, Reddy BS, Hayward-Sampson P, Tring IC, MacFie J. Randomized clinical trial of multi-modal optimization of surgical care in patients undergoing major colonic resection. *Br J Surg* 2005; 92(11):1354-1362.

70. Henriksen MG, Hansen HV, Hessov I. Early oral nutrition after elective colorectal surgery: influence of balanced analgesia and enforced mobilization. *Nutrition* 2002; 18(3):263-267.
71. Henriksen MG, Jensen MB, Hansen HV, Jespersen TW, Hessov I. Enforced mobilization, early oral feeding, and balanced analgesia improve convalescence after colorectal surgery. *Nutrition* 2002; 18(2):147-152.
72. Anderson AD, McNaught CE, MacFie J, Tring I, Barker P, Mitchell CJ. Randomized clinical trial of multimodal optimization and standard perioperative surgical care. *Br J Surg* 2003; 90(12):1497-1504.
73. Jakobsen DH, Sonne E, Andreassen J, Kehlet H. Convalescence after colonic surgery with fast-track vs conventional care. *Colorectal Dis* 2006; 8(8):683-687.
74. Holm B, Kehlet H. Physiotherapy after knee replacement - current practice vs. scientific evidence. (submitted). *Ugeskr Laeger* 2008.
75. Moffet H, Collet JP, Shapiro SH, Paradis G, Marquis F, Roy L. Effectiveness of intensive rehabilitation on functional ability and quality of life after first total knee arthroplasty: A single-blind randomized controlled trial. *Arch Phys Med Rehabil* 2004; 85(4):546-556.
76. Geerts WH, Pineo GF, Heit JA et al. Prevention of venous thromboembolism: the Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. *Chest* 2004; 126(3 Suppl):338S-400S.
77. Hull RD, Pineo GF, Stein PD et al. Extended out-of-hospital low-molecular-weight heparin prophylaxis against deep venous thrombosis in patients after elective hip arthroplasty: a systematic review. *Ann Intern Med* 2001; 135(10):858-869.
78. Bergqvist D. Venous thromboembolism: a review of risk and prevention in colorectal surgery patients. *Dis Colon Rectum* 2006; 49(10):1620-1628.
79. Sachs RA, Smith JH, Kuney M, Paxton L. Does anticoagulation do more harm than good?: A comparison of patients treated without prophylaxis and patients treated with low-dose warfarin after total knee arthroplasty. *J Arthroplasty* 2003; 18(4):389-395.
80. Sharrock NE, Gonzalez D, V, Go G, Lyman S, Salvati EA. Potent anticoagulants are associated with a higher all-cause mortality rate after hip and knee arthroplasty. *Clin Orthop Relat Res* 2008; 466(3):714-721.
81. Pearse EO, Caldwell BF, Lockwood RJ, Hollard J. Early mobilisation after conventional knee replacement may reduce the risk of postoperative venous thromboembolism. *J Bone Joint Surg Br* 2007; 89(3):316-322.
82. Salvati EA, Sharrock NE, Westrich G, Potter HG, Valle AG, Sculco TP. The 2007 ABJS Nicolas Andry Award: three decades of clinical, basic, and applied research on thromboembolic disease after THA: rationale and clinical results of a multimodal prophylaxis protocol. *Clin Orthop Relat Res* 2007; 459:246-254.
83. American Academy of Orthopaedic Surgeons Clinical Guideline on prevention of symptomatic pulmonary embolism in patients undergoing total hip or knee arthroplasty. [www.aaos.org/Research/guidelines/PE\\_guideline.pdf](http://www.aaos.org/Research/guidelines/PE_guideline.pdf) . 2008.
84. Borris LC, Breindahl M, Ryge C, Sommer HM, Lassen MR. Prothrombin fragment 1+2 in urine as an indicator of sustained coagulation activation after total hip arthroplasty. *Thromb Res* 2007; 121(3):369-376.
85. Johnson T, Monk T, Rasmussen LS et al. Postoperative cognitive dysfunction in middle-aged patients. *Anesthesiology* 2002; 96(6):1351-1357.
86. Monk TG, Weldon BC, Garvan CW et al. Predictors of cognitive dysfunction after major noncardiac surgery. *Anesthesiology* 2008; 108(1):18-30.

87. Rasmussen LS, Johnson T, Kuipers HM et al. Does anaesthesia cause postoperative cognitive dysfunction? A randomised study of regional versus general anaesthesia in 438 elderly patients. *Acta Anaesthesiol Scand* 2003; 47(3):260-266.
88. Maze M, Cibelli M, Grocott HP. Taking the lead in research into postoperative cognitive dysfunction. *Anesthesiology* 2008; 108(1):1-2.
89. Canet J, Raeder J, Rasmussen LS et al. Cognitive dysfunction after minor surgery in the elderly. *Acta Anaesthesiol Scand* 2003; 47(10):1204-1210.
90. Onen SH, Onen F, Courpron P, Dubray C. How pain and analgesics disturb sleep. *Clin J Pain* 2005; 21(5):422-431.
91. Rosenberg-Adamsen S, Kehlet H, Dodds C, Rosenberg J. Postoperative sleep disturbances: mechanisms and clinical implications. *Br J Anaesth* 1996; 76(4):552-559.
92. Gogenur I, Middleton B, Burgdorf S, Rasmussen LS, Skene DJ, Rosenberg J. Impact of sleep and circadian disturbances in urinary 6-sulphatoxymelatonin levels, on cognitive function after major surgery. *J Pineal Res* 2007; 43(2):179-184.
93. Cremeans-Smith JK, Millington K, Sledjeski E, Greene K, Delahanty DL. Sleep disruptions mediate the relationship between early postoperative pain and later functioning following total knee replacement surgery. *J Behav Med* 2006; 29(2):215-222.
94. Spath-Schwalbe E, Hansen K, Schmidt F et al. Acute effects of recombinant human interleukin-6 on endocrine and central nervous sleep functions in healthy men. *J Clin Endocrinol Metab* 1998; 83(5):1573-1579.
95. Rasmussen LS, Larsen K, Houx P, Skovgaard LT, Hanning CD, Moller JT. The assessment of postoperative cognitive function. *Acta Anaesthesiol Scand* 2001; 45(3):275-289.
96. The Danish Hip Arthroplasty Register. Available from: [www.dhr.dk](http://www.dhr.dk). Danish Ortopaedic Commondatabase . 2008.
97. Toms AD, Davidson D, Masri BA, Duncan CP. The management of peri-prosthetic infection in total joint arthroplasty. *J Bone Joint Surg Br* 2006; 88(2):149-155.
98. Tsukayama DT, Estrada R, Gustilo RB. Infection after total hip arthroplasty. A study of the treatment of one hundred and six infections. *J Bone Joint Surg Am* 1996; 78(4):512-523.
99. Callaghan JJ, Katz RP, Johnston RC. One-stage revision surgery of the infected hip. A minimum 10-year followup study. *Clin Orthop Relat Res* 1999;(369):139-143.
100. Hanssen AD, Spangehl MJ. Treatment of the infected hip replacement. *Clin Orthop Relat Res* 2004;(420):63-71.
101. Azodi OS, Adami J, Lindstrom D, Eriksson KO, Wladis A, Bellocco R. High body mass index is associated with increased risk of implant dislocation following primary total hip replacement: 2,106 patients followed for up to 8 years. *Acta Orthop* 2008; 79(1):141-147.
102. Mauerhan DR, Lonergan RP, Mokris JG, Kiebzak GM. Relationship between length of stay and dislocation rate after total hip arthroplasty. *J Arthroplasty* 2003; 18(8):963-967.
103. Peak EL, Parvizi J, Ciminiello M et al. The role of patient restrictions in reducing the prevalence of early dislocation following total hip arthroplasty. A randomized, prospective study. *J Bone Joint Surg Am* 2005; 87(2):247-253.

104. Smabrekke A, Espehaug B, Havelin LI, Furnes O. Operating time and survival of primary total hip replacements: an analysis of 31,745 primary cemented and uncemented total hip replacements from local hospitals reported to the Norwegian Arthroplasty Register 1987-2001. *Acta Orthop Scand* 2004; 75(5):524-532.
105. Karrholm J, Borssen B, Lowenhielm G, Snorrason F. Does early micromotion of femoral stem prostheses matter? 4-7-year stereoradiographic follow-up of 84 cemented prostheses. *J Bone Joint Surg Br* 1994; 76(6):912-917.
106. Baad-Hansen T, Kold S, Kaptein BL, Soballe K. High-precision measurements of cementless acetabular components using model-based RSA: An experimental study. *Acta Orthopaedica* 2007; 78(4):463-469.
107. Soballe K, Toksvig-Larsen S, Gelineck J et al. Migration of hydroxyapatite coated femoral prostheses. A Roentgen Stereophotogrammetric study. *J Bone Joint Surg Br* 1993; 75-B(5):681-687.
108. Borlin N, Thien T, Karrholm J. The precision of radiostereometric measurements. Manual vs. digital measurements. *J Biomech* 2002; 35(1):69-79.
109. Kiss J, Murray DW, Turner-Smith AR, Bulstrode CJ. Roentgen stereophotogrammetric analysis for assessing migration of total hip replacement femoral components. *Proc Inst Mech Eng [H ]* 1995; 209(3):169-175.
110. Ryd L, Albrektsson BE, Carlsson L et al. Roentgen stereophotogrammetric analysis as a predictor of mechanical loosening of knee prostheses. *J Bone Joint Surg Br* 1995; 77(3):377-383.
111. Karrholm J, Herberts P, Hultmark P, Malchau H, Nivbrant B, Thanner J. Radiostereometry of hip prostheses. Review of methodology and clinical results. *Clin Orthop Relat Res* 1997;(344):94-110.
112. Larsen K., Hansen TB, Thomsen PB, Christiansen T, Soballe K. Cost-efficiency of accelerated perioperative care and rehabilitation intervention after total hip and knee arthroplasty. *J Bone Joint Surg Am*. In press.

## Appendix 1: CV and list of publications of the two principal investigators

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### Personal data

Name: **Henrik Kehlet**  
Date of birth: 9<sup>th</sup> March 1942  
Private address: Stoltenbergsgade 5, DK-1576 Copenhagen  
Work address: Section for Surgical Pathophysiology, Rigshospitalet, Blegdamsvej 9, DK-2100 Copenhagen  
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### Education

1968: MD, University of Copenhagen, Denmark  
1977: PhD, University of Copenhagen, Denmark  
1980: Specialist in Surgery and Surgical Gastroenterology

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### Scientific positions

1989-2004: Chief Surgeon, Department of Surgery, Hvidovre University Hospital  
1991-2005: Professor of Surgery, University of Copenhagen  
2004- Head, Section for Surgical Pathophysiology, Rigshospitalet, Copenhagen  
2006- Professor of Perioperative Therapy, University of Copenhagen

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### Bibliography

Peer-reviewed papers: >700 (>580 of which are on PubMed)  
Citations: ~13000, about 1000/yr since 2000  
H-index: 63  
Invited lectures: ~250 (international scientific meetings)

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### Supervisor Experience

Doctoral dissertations: > 12 MD theses (HK personal supervisor)

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### Awards

Honorary awards and lectures:  
Honorary Doctor, Linköping University, Sweden 1987  
Honorary Fellow, Royal College of Anaesthetists, England 1995  
Honorary Fellow, American College of Surgeons, US 2003  
Honorary Fellow of the German Surgical Society, Germany, 2005  
Honorary Member of the Chilean Surgical Society, Chile 2006  
Honorary Member of the Chilean Colorectal Society, Chile 2006  
Honorary Member of the German Society of Anaesthesiology and Intensive Care, Germany 2007

> 20 major named honorary lectures, including:

The Labat Lecture, American Society of Regional Anesthesia, Toronto, Canada, 2005  
The Rupert B Turnbull Memorial Oration, Cleveland Clinic, Cleveland, US, 2005  
The Theodor Kocher Lecture, Berne University, Switzerland, 2005

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The Harry E Bacon Lecture, American Society of Colon and Rectal Surgeons, Seattle, US 2006  
The International Surgery Lecture, American College of Surgeons, Chicago, US 2006  
The Nicoll Lecture, International Association for Ambulatory Surgery, Amsterdam, Holland 2007  
The British Journal of Surgery Lecture, Society of Academic Surgeons, Birmingham, England 2008  
The Annual Lecture, American Society of Ambulatory Anesthesia Frontier Lecture, Miami, US 2008

Selected other Honorary Awards

The Novo-Nordic Award 1996  
The August Krogh Award 2000  
The Gimbernet Prize, Catalan Surgical Society, Spain 2007

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**List of publications (last 3 years)**

1. Kehlet H, Gray A, Bonnet F, Camu F, Fisher B, McCloy R, Puig MM, Rawal N, Simanski C, Neugebauer E. A systematic qualitative and quantitative review of analgesic, anesthetic and operative techniques for postoperative pain relief following laparoscopic cholecystectomy. *Surgical Endoscopy* 2005; 9: 1396-1415.
2. Bisgaard T, Rosenberg J, Kehlet H. From acute to chronic pain after laparoscopic cholecystectomy – a prospective follow-up study. *Scandinavian Journal of Gastroenterology* 2005;40: 1358-1364
3. Kehlet H. Procedure specific postoperative pain management. *Anesthesiology Clinics of North America* 2005;23: 203-210.
4. Aasvang E, Kehlet H. Chronic postoperative pain – the case of inguinal herniorrhaphy. *British Journal of Anaesthesia* 2005;95: 69-75
5. Kehlet H, Aasvang E. Anesthesia for groin hernia repair. *World Journal of Surgery* 2005;29: 1058-1061
6. Kehlet H, Bay-Nielsen M. Anaesthesia for hernia surgery in Denmark 1998-2003. *Acta Anaesthesiologica Scandinavica* 2005;49: 143-146
7. Kehlet H, Williamson R, Büchler MW, Beart RW, A survey of perceptions and attitudes among European surgeons of the clinical impact and management of postoperative ileus. *Colorectal Disease* 2005;7: 245-250.
8. Brennan TJ, Kehlet H. Preventive analgesia to reduce wound hyperalgesia and persistent postoperative pain – not an easy path. *Anesthesiology* 2005;103: 681-683.
9. Gray A, Kehlet H, Bonnet F, Rawal N. Predicting postoperative analgesia outcomes: NNT League tables or procedure-specific evidence? *British Journal of Anaesthesia* 2005;94: 710-714
10. Heidemann Andersen F, Nielsen K, Kehlet H. Combined ileoinguinal blockade and local infiltration anaesthesia for inguinal hernia repair – a double blind randomised study. *British Journal of Anaesthesia* 2005;94: 520-523.
11. Carli F, Kehlet H. Continuous epidural analgesia for colonic surgery – years from now, but what about the future? *Regional Anesthesia and Pain Medicine* 2005;30: 140-142
12. Kehlet H, Wilmore DW. Fast-track surgery. *British Journal of Surgery* 2005;92: 3-4.
13. Foss NB, Kristensen MT, Kristensen BB, Jensen PS, Kehlet H. Effect of postoperative epidural analgesia on rehabilitation and pain after hip fracture surgery: a randomised double-blind, placebo-controlled trial. *Anesthesiology* 2005;102: 1197-1204
14. Kristensen MT, Foss NB, Kehlet H. Timed up and go og new mobility score til prædiktation af function 6 måneder efter hoftefraktur. *Ugeskrift for Læger* 2005;167: 3297-3301
15. Kehlet H. Effects of postoperative pain relief on outcome. In: *Pain 2005 – an updated review* ed. DM Justins. IASP Press, Seattle, 2005 p 277-281.
16. Aasvang E, Kehlet H. Surgical treatment of chronic post-herniorrhaphy pain *British Journal of Surgery* 2005;92: 795-801
17. Wara P, Bay-Nielsen M, Juul P, Bendix J, Kehlet H. Laparoscopic compared with Lichtenstein repair of inguinal hernia. A prospective nation-wide analysis. *British Journal of Surgery* 2005;92: 1277-1281.

18. Kehlet H. Postoperative opioid-sparing to improve outcome – what are the issues? *Anesthesiology* 2005;102: 1083-1085
19. Kehlet H. Fast-track colonic surgery – status and perspectives. *Recent Results Cancer Research* 2005;165: 8-13
20. Basse L, Jakobsen DH, Bardram L, Billesbølle P, Lund C, Mogensen T, Rosenberg J, Kehlet H. Functional recovery after open vs laparoscopic colonic surgery. A randomised blinded study. *Annals of Surgery* 2005;241: 416-423
21. Andersen J, Kehlet H. Fast-track open ileo-colic resections for Crohn's disease. *Colorectal Disease* 2005;7: 394-397
22. Fearon K, Ljungqvist O, Meyenfeldt MV, Revhaug A, de Jong K, Lassen K, Nygren J, Hausel J, Soop M, Andersen J, Kehlet H. Enhanced recovery after surgery: A consensus review of clinical care for patients undergoing colonic resection. *Clinical Nutrition* 2005;24: 466-477
23. Kristensen MT, Foss NB, Kehlet H. The cumulated ambulation score: en postoperativ score til prædiktion af tidlig rehabilitering og morbiditet hos hoftefrakturpatienter. *Fysioterapeuten* 2005;5: 22-26
24. Foss NB, Kehlet H. Mortality analysis in hip fracture patients, implications for design for future trials. *British Journal of Anaesthesia* 2005;94: 24-29.
25. Kehlet H. Bare et hernie – for sidste gang? (Editorial) *Ugeskrift for Læger* 2005;167: 1372
26. Nygren J, Hausel J, Kehlet H, Revhaug A, Lassen K, Dejong C, Andersen J, von Meyenfeldt M, Fearon K, Ljungqvist O. A comparison in 5 European centres of case mix, clinical management and outcomes following either conventional or fast-track perioperative care in colorectal surgery. *Clinical Nutrition* 2005;24: 455-461
27. Dahl JB, Kehlet H. Postoperative pain and its management in "Melzack and Wall Textbook of Pain". (McMachon and Kolzenburg, eds.) Elsevier, Amsterdam 2005 p 635-651.
28. Werner MU, Gaarn-Larsen L, Basse L, Jakobsen DH, Lund C, Billesbølle P, Kehlet H. Postoperative pain and gastrointestinal recovery after colonic resection with epidural analgesia and multi-modal rehabilitation. *Acute Pain* 2005;7: 5-11
29. Holte K, Kehlet H. Postoperative ileus. *Månedsskrift for Praktisk Lægegerning* 83: 201-206
30. Bardram L, Klarskov B, Rosenberg J, Lund C, Kehlet H. Ambulant laparoskopisk kolecystektomi – 2 års erfaring *Ugeskrift for Læger* 2005;167: 2644-2648
31. Foss NB, Palm H, Kehlet H. In-hospital hip fracture: prevalence, risk factors and outcome *Age and Ageing* 2005;34: 642-645.
32. Kehlet H, Jakobsen DH, Herlufsen P(2005) *Gastroenterologi i "Kirurgi-sygdomslære og sygepleje"*. Nyt Nordisk Forlag, 2. udgave, 2005 p 190-242
33. Jakobsen DH, Kehlet H. *Kirurgisk sygepleje i "Kirurgi-sygdomslære og sygepleje"*. Nyt Nordisk Forlag, 2. udgave, 2005 p 21-46
34. Kehlet H. Optimeret patientforløb ved kolorektal cancer. *Ugeskrift for Læger* 167: 4185-4186.
35. Kehlet H. Postoperative pain. In: *American College of Surgery: Perioperative Care; Principles and Practice* Souba W, Fink MP, Jurkovic GJ et al. (eds) WebMD Inc, New York 2005;5: 1-15
36. Lauritsen M, Bendixen A, Jensen LS, Svendsen LB, Kehlet H. Ventrikelresektion for cancer i Danmark 1999-2004. *Ugeskrift for Læger* 2005;167: 3048-3051
37. Kehlet H. Organisation of surgery in Denmark. (Editorial) (in Danish) *Ugeskrift for Læger* 2005;167: 4155
38. Kehlet H. Preventive measures to minimize or avoid postoperative ileus. *Seminars in Colon & Rectal Surgery* 2005;16:203-207
39. Aasvang EK, Møhl B, Bay Nielsen M, Kehlet H. Pain related sexual dysfunction after groin hernia repair. *Pain* 2006;122:258-263
40. Bay Nielsen M, Kehlet H. Inguinal herniorrhaphy in women *Hernia* 2006;10:30-33
41. Jakobsen DH, Sonne E, Kehlet H. Fast-track colonic surgery – the effect on nursing workload. *Journal of Advanced Perioperative Care* 2006;2:177-181
42. Bitsch MS, Foss NB, Kristensen BB, Kehlet H. Acute cognitive dysfunction after hip fracture: Incidence and risk factors in an optimised, multimodal rehabilitation programme. *Acta Anaesthesiologica Scandinavica* 2006;50:428-436

43. Jakobsen DH, Sonne E, Andreasen J, Kehlet H. Convalescence after colonic surgery with fast-track versus conventional care. *Colorectal Disease* 2006;8:683-687
44. Husted H, Holm G, Rud K, Bach-Dal C, Hansen HC, Kehlet H. Hospital stay after hip and knee arthroplasty in Denmark 2001-2003. (in Danish) *Ugeskrift for Læger* 2006;168:276-279
45. Marx C, Rasmussen T, Jakobsen DH, Ottosen C, Lundvall L, Ottesen B, Callesen T, Kehlet H. The effect of accelerated rehabilitation on recovery after surgery for ovarian malignancy. *Acta Obstetrica et Gynecologica Scandinavica* 2006;85:488-492
46. Kehlet H, Büchler MW, Beart RW, Billingham RP, Williamson R. Care after colonic surgery – is it evidence-based? Results from a multi-national survey in Europe and the USA. *Journal of American College of Surgeons* 2006;202:45-54
47. Foss NB, Christensen DS, Krasheninnikoff M, Kristensen BB, Kehlet H. Postoperative rounds by anaesthetists after hip fracture surgery: A pilot study. *Acta Anaesthesiologica Scandinavica* 2006;50:437-442
48. Kehlet H, Jensen TS, Woolf CS. Postsurgical persistent pain and risk factors and prevention. *Lancet* 2006;367:1618-1625
49. Nikolajsen L, Brandsburg B, Lucht O, Jensen T, Kehlet H. Chronic pain following total hip arthroplasty: A nationwide questionnaire study. *Acta Anaesthesiologica Scandinavica* 2006;50:495-500
50. Foss NB, Kristensen MT, Kehlet H. Prediction of postoperative rehabilitation and mortality in hip fracture patients: the cumulated ambulation score. *Clinical Rehabilitation* 2006;20:701-708
51. Holte K, Kehlet H. Fluid therapy and surgical outcome in elective surgery – a need for reassessment in fast-track surgery. A systematic review. *Journal of American College of Surgeons* 2006;202:971-989
52. Kehlet H, Kennedy R. Laparoscopic colonic surgery – mission accomplished or work in progress? *Colorectal Disease* 2006;8: 514-517
53. Foss NB, Kehlet H. Short-term mortality in hip fracture patients admitted during weekends and holidays. *British Journal of Anaesthesia* 2006;96:450-454
54. Kehlet H. Surgical stress and outcome – from here to where? (Labat lecture) *Regional Anesthesia and Pain Medicine* 2006;31:47-52
55. Husted H, Hansen HC, Holm G, Bach-Dal C, Rud K, Andersen KL, Kehlet H. Hospital stay after hip and knee arthroplasty – relation to volume, morbidity, mortality and resources. A nation-wide study in Denmark. (in Danish) *Ugeskrift for Læger* 2006;168:2139-2143
56. Husted H, Hansen HC, Holm G, Bach-Dal C, Rud K, Andersen KL, Kehlet H. Short vs. long hospital stay after hip and knee arthroplasty – organizational and professional aspects. A nation-wide study in Denmark. (in Danish) *Ugeskrift for Læger* 2006;168:2144-2148
57. Husted H, Hansen HC, Holm G, Bach-Dal C, Rud K, Andersen KL, Kehlet H. Patient satisfaction after hip and knee arthroplasty with short vs. long hospital stay. A nation-wide study in Denmark. (in Danish) *Ugeskrift for Læger* 2006;168:2148-2151
58. Dahl JB, Kehlet H. Acute postoperative pain – a status report. (in Danish) *Ugeskrift for Læger* 2006;168:1986-1988
59. Aasvang EK, Bay-Nielsen M, Kehlet H. Pain and functional impairment six years after inguinal herniorrhaphy. *Hernia* 2006;10:316-322
60. Jensen TS, Kehlet H. Chronic postoperative pain. (in Danish) *Ugeskrift for Læger* 2006;168:1989-1991
61. Marx C, Møller C, Bendixen A, Kehlet H, Ottesen B. Ovarian cancer in Denmark: Status for the surgical treatment. (in Danish) *Ugeskrift for Læger* 2006;168:1537-1540
62. Marx C, Rasmussen T, Hjort-Jacobsen D, Ottosen C, Lundvall L, Ottesen B, Callesen T, Kehlet H. Fast-track surgery for ovarian cancer. (in Danish) *Ugeskrift for Læger* 2006;168:1533-1536
63. Foss NB, Kehlet H. Hidden blood loss after hip fracture surgery. *Journal of Bone and Joint Surgery* 2006;88:1053-1059
64. Kehlet H, Laurberg S. Gastrointestinal surgery – why specialisation? (in Danish) *Ugeskrift for Læger* 2006;168:1519-1521

65. Kehlet H. Laparoscopic surgery – strategies for future improvement in outcome. In "Guidelines for endoscopic surgery. Twelve years evidence-based surgery in Europe." Neugebauer, Sauerland, Fingerhut, Millat and Buess (eds.) Springer Verlag, Heidelberg 2006 p 401-403
66. Firoozfard B, Christensen T, Bendixen A, Nordling S, Kehlet H. Nephrectomy in Denmark 2002-2005 (in Danish) Ugeskrift for Læger 2006;168:1526-1528
67. Kehlet H, Sindrup S. Pain – it hurts in many places (editorial) (in Danish) Ugeskrift for Læger 2006;168:1939
68. Kupers R, Kehlet H. Brain imaging of chronic pain states: a critical review and strategies for future studies *Lancet Neurology* 2006;5:1033-1044
69. Kehlet H. Future perspectives and research initiatives in fast-track surgery. *Langenbeck's Archives of Surgery* 2006;391:495-498
70. Kehlet H. Fast-track surgery – the facts and the challenges. *Cirurgia Espanola* 2006;80:187-188
71. Kehlet H, Dahl JB. Why is surgery risky? (in Danish) Ugeskrift for Læger 2006;168:4291-4292
72. Kehlet H. Monitoring of surgical quality – status and proposal for a national strategy (in Danish) Ugeskrift for Læger 2006;168:4324-4327
73. Palm H, Jacobsen S, Krashninnikoff M, Foss NB, Kehlet H, Gebuhr P.. The role of surgeon experience and supervision on outcome after hip fracture surgery. *Injury* 2007;38:775-779
74. Foss NB, Palm H, Krashninnikoff M, Kehlet H, Gebuhr P.. The impact of surgical complications on length of stay after hip fracture surgery. *Injury* 2007;38:780-784
75. Röstlund T, Kehlet H. High-dose local infiltration analgesia after hip and knee replacement – what is it; why does it work and what are the future challenges? *Acta Orthopædica* 2007;78:159-161
76. Maessen J, Dejong CHC, Hausel J, Nygaard J, Lassen K, Andersen J, Kessels AGH, Revhaug A, Kehlet H, Ljungqvist O, Fearon KCH, von Meyenfeldt MF. Implementation of an enhanced recovery programme for colorectal resection: Is a protocol enough? *British Journal of Surgery* 2007;94:224-231
77. Kristensen MT, Foss NB, Kehlet H. Timed up & go test as a predictor of falls within six months after hip fracture surgery. *Physical Therapy* 2007;87:24-30
78. Aasvang EK, Kehlet H. Chronic pain after childhood groin hernia repair *Journal of Pediatric Surgery* 2007;42:1403-1408
79. Holte K, Kristensen BB, Valentiner L, Foss NB, Husted H, Kehlet H. Liberal vs restrictive fluid management in knee arthroplasty: A randomised blinded study *Anesthesia and Analgesia* 2007;105:465-474
80. Holte K, Hahn RG, Ravn L, Bertelsen KG, Hansen S, Kehlet H. The influence of liberal vs. restrictive intraoperative fluid administration on elimination of a postoperative fluid load *Anesthesiology* 2007;106:75-79
81. Foss NB, Kristensen BB, Bundgaard M, Bak M, Heiring C, Virkelyst C, Hougaard S, Kehlet H. Fascia iliaca blockade for acute pain control in hip fracture patients: a randomized, placebo-controlled trial *Anesthesiology* 2007;106:773-778
82. Neugebauer E, Wilkinson R, Kehlet H, Schug S. PROSPECT: a practical method for formulating evidence-based expert recommendations for the management of postoperative pain. *Surgical Endoscopy* 2007;21:1047-1053
83. White PF, Kehlet H, Neal JM, Schricker T, Carr DB, Carli F. The role of anesthesiologists in fast-track surgery: from multimodal analgesia to perioperative medicine *Anesthesia & Analgesia* 2007;104:1380-1396
84. Jensen K, Kehlet H, Lund C. Postoperative recovery profile after laparoscopic cholecystectomy. A prospective, observational study of a multimodal anaesthetic technique. *Acta Anaesthesiologica Scandinavica* 2007;51:464-471
85. Bundgaard-Nielsen M, Holte K, Secher NH, Kehlet H. Monitoring of perioperative fluid administration by individualized goal-directed therapy *Acta Anaesthesiologica Scandinavica* 2007;51:331-340
86. Larsen TS, Schulze S, Kehlet H. Laparoscopic colorectal surgery in Denmark 2004-2005. (in Danish) Ugeskrift for Læger 2007;169:1089-1091
87. Holte K, Foss NB, Andersen J, Valentiner L, Lund C, Bie P, Kehlet H. Liberal vs restrictive fluid administration in fast-track colonic surgery: a randomised, blinded study *British Journal of Anaesthesia* 2007;99:500-508

88. Hansen CT, Sørensen M, Møller C, Ottesen B, Kehlet H. Effect of laxative on gastrointestinal functional recovery in fast-track hysterectomy. A double-blind, placebo-controlled, randomised study *American Journal of Obstetrics and Gynecology* 2007;196:311-317
89. Rasmussen S, Kehlet H. Management of nerves during leg amputation – a neglected area in our understanding of the pathogenesis of phantom limb pain *Acta Anaesthesiologica Scandinavica* 2007;51:1115-1116
90. Andersen J, Hjort-Jacobsen D, Christiansen PS, Kehlet H. Readmission rates after a planned 2- versus 3-day stay in fast-track colonic surgery *British Journal of Surgery* 2007;94:890-893
91. Aasvang EK, Møhl B, Kehlet H. Ejaculatory pain and sexual dysfunction following groin hernia repair – a specific pain syndrome? *Anesthesiology* 2007;107:298-304
92. Neugebauer E, Wilkinson R, Kehlet H. Transferable evidence in support of reaching a consensus. *Zeitschrift für Ärztliche Fortbildung in Qualität und Gesundheit*. 2007;101:103-107
93. Brandsborg B, Nikolajsen L, Hansen CT, Kehlet H, Jensen TS. Risk factors for chronic pain following hysterectomy. A nation-wide questionnaire and database study. *Anesthesiology* 2007;106:1003-1012
94. Rotbøll Nielsen P, Nørsgaard L, Rasmussen LS, Kehlet H. Prediction of postoperative pain by an electrical pain stimulation. *Acta Anaesthesiologica Scandinavica* 2007;51:582-587
95. Bundgaard-Nielsen M, Ruhnau B, Secher NH, Kehlet H. Flow-related techniques for preoperative goal-directed fluid optimisation. *British Journal of Anaesthesia* 2007;98:38-44
96. Kehlet H, Wilkinson RC, Fischer HBJ, Camu F. PROSPECT: evidence-based procedure-specific postoperative pain management. *Best Practice & Research Clinical Anaesthesiology* 21:149-159
97. Bisgaard T, Bay-Nielsen M, Christensen IS, Kehlet H. 2007;Risk of recurrence beyond 5 years after primary Lichtenstein mesh vs. sutured inguinal hernia repair. A prospective nation-wide study. *British Journal of Surgery* 2007;94:1038-1040
98. White PF, Kehlet H. Postoperative analgesia and outcome – time to return to work. *Anesthesia and Analgesia* 2007;104:487-489
99. Rud K, Jakobsen DH, Egerod I, Kehlet H. Guidelines for perioperative care after nephrectomy in Denmark (in Danish) *Sygeplejersken* 2007;12:56-59
100. Sørensen P, Holm MB, Christensen FT, Foss NB, Kehlet H. Optimized admittance procedure for patients with hip fracture (in Danish) *Ugeskrift for Læger* 2007;169:808-812
101. Schug SS, Kehlet H, Bonnet F, Camu F, Fischer B, Joshi G, Neugebauer EAM, Rawal N, Simanski C. Procedure specific pain management after surgery – PROSPECT. *Acute Pain* 2007;9:55-57
102. Jensen LS, Bendixen A, Kehlet H. Organisation and early outcomes of major upper gastrointestinal cancer surgery in Denmark 1996 – 2004. *Scandinavian Journal of Surgery* 2007;96:41-45
103. White PF, Kehlet H. Improving pain management: Are we jumping from the frying pan into the fire? *Anesthesia & Analgesia* 2007;105:10-12
104. Bay-Nielsen M, Kehlet H. How to create a hernia – Bassini. In: *Recurrent hernia – prevention and treatment* (eds: V Schumpelick and RJ Fitzgibbons) Springer Verlag, Berlin 2007 p. 255-257
105. Kehlet H, Bay-Nielsen M. Standard procedures for standard patients? In: *Recurrent hernia – prevention and treatment* (eds: V Schumpelick and RJ Fitzgibbons) Springer Verlag, Berlin 2007 p. 385-390
106. Kehlet H, Liu SS. Continuous local anesthetic wound infusion to improve postoperative outcome – back to the periphery? *Anesthesiology* 2007;107:369-371
107. Kehlet H. Glucocorticoids for perioperative analgesia – how far are we from general recommendations? *Acta Anaesthesiologica Scandinavica* 2007;51:1133-1136
108. Marx C, Bendixen A, Høgdall C, Ottosen C, Kehlet H, Ottesen B. Organisation and quality of the primary surgical intervention for ovarian cancer in Denmark. *Acta Obstetricia & Gynecologica Scandinavica* 2007;86:1496-1502
109. Simanski C, Kehlet H, Bonnet F, Camu F, Fisher B, Joshi G, Neugebauer EAM, Rawal N, Schug SA. Procedurenspezifische Akutschmerztherapie. *Minimal Invasive Chirurgie* 2007;16:123-129
110. Foss NB, Jensen PS, Kehlet H. Risk factors for insufficient perioperative oral nutrition after hip fracture within a multimodal rehabilitation programme. *Age and Ageing* 2007;36:538-543
111. Bay-Nielsen M, Kehlet H. Anaesthesia and postoperative morbidity after elective groin hernia repair – a nationwide study. *Acta Anaesthesiologica Scandinavica* 2008;52:169-174

112. Johansen L, Christensen TH, Bendixen A, Nordling J, Jensen KME, Kehlet H.. Cystectomy in Denmark 2000-2005. (in Danish) *Ugeskrift for Læger* 2008;170:215-217
113. Foss NB, Kristensen MT, Kehlet H. Anaemia impedes functional mobility after hip fracture surgery. *Age and Ageing* 2008;37:173-178
114. Holte K, Kehlet H. Perioperative fluid management – a status (in Danish) *Ugeskrift for Læger* 2008;170:1237-1239
115. Dworkin RH, Turk DC, Wyrach KW, Beaton D, Cleeland CS, Farrar JT, Haythoruthawaite JA, Jensen MP, Keus RD, Ader DN, Brandenburg N, Burke LB, Cella D, Chandler J, Cowan P, Dimitrova R, Dionne R, Hertz S, Jadad AR, Kutz NP, Kehlet H, Kramer LD, Manning DC, McCormick C, McDermott MP, McQuay HS, Patel S, Porter L, Quessey S, Rappaport BA, Rauschkolb C, Revicki DA, Rothman M, Schumacker KE, Stacey BR, Stauffer JW, van Stein T, White RE, Wither J, Zavisic S. Interpreting the clinical importance of treatment outcomes in chronic pain clinical trials: IMMPACT recommendations. *Journal of Pain* 2008;9:105-121
116. Funch-Jensen P, Bendixen A, Iversen MG, Kehlet H. Complications and frequency of redo antireflux surgery in Denmark. A nationwide study 1997-2005. *Surgical Endoscopy* 2008;22:627-630
117. Kehlet H, Bay Nielsen M. Nationwide quality improvement of groin hernia repair from the Danish Hernia Database of 87840 patients from 1998 – 2005) 2008; *Hernia* 12:1-7
118. Kehlet H. Clinical update: fast-track colorectal surgery. *Lancet* 371:791-793
119. Brandsborg B, Nikolajsen L, Kehlet H, Jensen TS. Chronic pain following hysterectomy – a review. *Acta Anaesthesiologica Scandinavica* 2008;52:327-331
120. Bisgaard T, Bay-Nielsen M, Kehlet H. Re-recurrence after operation form recurrent hernia: A nationwide eight years' follow-up study. *Annals of Surgery* 2008;247:707-711
121. Kehlet H. Kirurgisk kvalitet – hvad, hvordan og hvorfor? (in Danish) *Bibliotek for Læger* 2008;200:118-128
122. Kehlet H. Chronic pain after groin hernia repair. *British Journal of Surgery* 2008;95:135-136
123. Schulze S, Iversen MG, Stigaard Larsen T, Kehlet H. Laparoscopic colorectal surgery in Denmark 2004-2007. *Colorectal Disease* 2008 (Epub ahead of print) DOI:10.1111/j.1463-1318.2008.01497.x
124. Naert ALG, Kehlet H, Kupers R. Characterization of a novel model of tonic heat pain stimulation in healthy volunteers. *Pain* 2008 (Epub ahead of print) DOI:10.1016/j.pain.2007.11.018
125. Kehlet H, Bay-Nielsen, M. Local anaesthesia as a risk factor for recurrence after groin hernia repair? *Hernia* 2008 (Epub ahead of print) DOI:10.1007/s10029-008-0371-3
126. Aasvang EK, Brandsborg B, Christensen B, Jensen TS, Kehlet H.. Neurophysiological characterization of postherniorrhaphy pain. *Pain* 2008 (Epub ahead of print) DOI:10.1016/j.pain.2007.09.026
127. Aasvang EK, Hansen EB, Malmstrøm J, Asmussen T, D. Gennevois, Kehlet H. Effect of capsaicin wound instillation on post-heriotomy pain – a double-blind randomized study. *Anesthesia and Analgesia* 2008 (in press)
128. Ljungmann K, Bendixen A, Laurberg S, Kehlet H. Organisation og tidlige operationsresultater efter ileo-pouch-anal kirurgi i Danmark 2001-2005. *Ugeskrift for Læger* 2008; (in press)
129. Aasvang EK, Kehlet H. Postherniorrhaphy dysejaculation: successful treatment with mesh removal and nerve transaction. *Hernia* 2008 (in press)
130. Borre M, Iversen P, Bendixen A, Kehlet H. Organisation and early outcome after radical prostatectomy in Denmark 2004 – 2007. *Ugeskrift for Læger* 2008 (in press)
131. Rud K, Hjort Jakobsen D, Egerod I, Kehlet H. Implementation of surgical procedure-specific guidelines. *Ugeskrift for Læger* 2008 (in press)
132. Andersen LØ, Husted H, Otte KS, Kristensen BB, Kehlet H. A compression bandage prolongs duration of local infiltration analgesia in total knee arthroplasty. *Acta Orthopaedica* 2008 (in press)
133. Andersen LØ, Kristensen BB, Husted H, Otte KS, Kehlet H. Local anesthetics after total knee arthroplasty: intra- vs. extraarticular administration? A randomised double-blind study. *Acta Orthopaedica* 2008 (in press)
134. Kristensen MT, Bandholm T, Foss NB, Ekdahl C, Kehlet H. Reliability of the New Mobility Score in hip hip fracture patients. *Journal of Rehabilitation Medicine* 2008 (in press)

135. Hansen CT, Møller C, Daugbjerg S, Utzon J, Kehlet H, Ottesen B. Establishment of a national Danish hysterectomy database: preliminary report of the first 13425 hysterectomies. *Acta Gynecologica et Obstetrica Scandinavica* 2008 (in press)
136. Gärtner R, Kroman N, Callesen T, Kehlet H. Multimodal smertebehandling ved brystkræftkirurgi. *Ugeskrift for Læger* 2008 (i trykken)
137. Gärtner R, Kroman N, Callesen T, Kehlet H. Optimering af det tidlige forløb efter brystkræftkirurgi. *Ugeskrift for Læger* 2008 (i trykken)
138. Kehlet H. The role of the anesthesiologist in fast-track surgery. *Anesthesia & Analgesia* 2008 (in press)
139. Kehlet H, Wilmore DW. Evidence-based surgical care and the evolution of fast-track surgery. *Annals of Surgery* 2008 (in press)
140. Fischer HBJ, Simanski CJP, Sharp C, Bonnet F, Camu F, Neugebauer EAM, Rawal N, Joshi GP, Schug SA, Kehlet H. A procedure-specific systematic review and consensus recommendations for postoperative analgesia following total knee arthroplasty. *Anaesthesia* 2008 (in press)
141. Joshi G, Bonnet F, Shah R, Wilkinson RC, Camu F, Fisher B, Neugebauer EA, Rawal N, Shug S, Kehlet H. A systematic review to evaluate the efficacy and safety of regional analgesic techniques for post-thoracotomy analgesia. *Anesthesia & Analgesia* 2008 (in press)

### Personal data

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### Education

1983: MD, University of Aarhus, Denmark  
1994: DMSc, University of Aarhus, Denmark  
1994: Specialist in Orthopaedic surgery

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### Scientific positions

1987: Research Fellowship in Orthopaedics, Aarhus University Hospital  
1994: Research and clinical fellowship, Dept. of Orthopaedics, University of Minnesota, USA  
1998: Associate Professor, University Hospital of Aarhus  
1998: Associate Professor, Danish Institute for Health Technology Assessment (DIHTA)  
1998: Nominated number one for a full clinical professorship in Orthopaedics, University of Copenhagen  
2000: Chief Surgeon, Department of Orthopaedics, Aarhus University Hospital  
2001: Clinical Professor in Orthopaedics, Aarhus University Hospital (5 years)  
2003: Honorary Professor, Department of Orthopaedic Surgery, University of Minnesota, USA  
2005: Full Clinical Professorship in Orthopaedic Surgery, Aarhus University Hospital  
2007: Head of graduate programme within clinical medicine, University of Aarhus

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### Bibliography

Peer-reviewed papers: 182 (174 of which are on PubMed)  
Citations: 2559  
H-index: 27  
Invited lectures: 119  
Book chapters: 8  
Book chapters in teaching books: 2

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### Supervisor Experience

PhD projects: 14 completed  
PhD projects: 27 in progress  
Doctoral dissertations: 4 completed  
Doctoral dissertations: 4 in progress  
Diploma projects: 27 completed  
Diploma projects: 5 in progress

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### **Member of evaluation of scientific theses**

|                 |           |
|-----------------|-----------|
| DMSc theses:    | 4 theses  |
| PhD theses:     | 19 theses |
| Diploma theses: | 27 theses |

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### **Selection Committee**

Professor of orthopaedics, University of Aarhus, 2007  
Professor of orthopaedics, University of Oslo, Norway, 2004  
Professorship in sensory motor function, Aarhus University Hospital, 2004  
Professorship in pathology, University of Aarhus, 2004  
Associated professorship, University of Aarhus, 2003  
Associated professorship, University of Aarhus, 2002

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### **Current research interest**

Experimental basic research in implant fixation, ceramic coatings, bone grafting, growth factors, cytokines, wear debris, nano science, tissue engineering, therapeutic peptides, gene technology, clinical studies of total joints, epidemiology of osteoarthritis, clinical databases, stem cells

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### **Awards**

European Society of Biomechanics (ESB) Research Award for 1996  
Young investigator award. Orthopaedic Research Society, Atlanta, 1997  
Young investigator award. Combined Orthopaedic Research Society Meeting, Hamamatsu, Japan, 1997  
European Society for Biomaterials award. Amsterdam, 1988  
Award paper (best lecture), Danish Orthopaedic Society, Copenhagen, 1998  
Award paper. Danish Orthopaedic Society, 2000, 2001, 2002, 2004, 2005, 2007  
Award paper. Hip International, Baveno 2002  
Acta Orthopaedica Scandinavica Award article year 2000 (10,000 USD)  
Acta Orthopaedica Scandinavica Award article, 2002 (10,000 USD)  
William Harris Award, Washington DC, 2005 (5,000 USD)  
Kappa Delta Award, Orthopaedic Research Society 2005 and 2007  
Best Poster Award, PhD Day, Aarhus University, 2006 and 2007

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### **List of publications (last 3 years)**

#### **2005**

1. Kold S, Bechtold J, Mouzin O, Bourgeault C, Søballe K. Importance of preclinical testing exemplified by femoral fractures in vitro with new bone preparation technique, *Clinical Biomechanics* 20, 77-82; 2005
2. Kold S, Rahbek, Vestermark MT, Overgaard S, Søballe K. Bone compaction enhances fixation of weight-bearing titanium implants *Clin Orthop*,2005;431:138-144
3. Elmengaard B, Bechtold J, Søballe K. In vivo study of the effect of RGD-treatment on bone ongrowth on press-fit titanium alloy implants. *Biomaterials*, 26: 3521-6; 2005
4. Jensen, TB, Rahbek O, Overgaard S, Søballe K. No effect of platelet-rich plasma with frozen or processed bone allograft around noncemented implants. *Int Orthop*,2005;29:67-72
5. Pedersen AB, Johnsen SP, Søballe K, Overgaard S, Sørensen HT, Lucht U Regional variation in incidence of primary total hip arthroplasties and revisions in Denmark 1996-2002. *Acta Orthop*. 2005;76:182-9

6. Ito H, Koefoed M, Tiyyapatanaputi P, Gromov K, Goater J, Carmouche J, Zhang X, Rubery P, Nakamura T, Søballe K, O'Keefe R, Schwarz E. Remodeling of cortical bone allografts mediated by adherent rAAV-RANKL and VEGF gene therapy. *Nat Med*, 2005, 11, 291-297
7. Jacobsen S, Sonne-Holm S, Søballe K, Gebuhr P, Lund B. Hip dysplasi and osteoarthritis. A survey of 4151 subjects from the Osteoarthritis substudy of the Copenhagen City Heart Study. *Acta Orthop Scand* 2005;76: 149-158
8. Kold S, Bechtold J, Mouxin O, Elmengaard B, Chen X, Søballe K. Fixation of revision implants is improved by a surgical technique to crack the sclerotic bone rim. *Clin Orthop Relat Res*, 2005;432:160-166
9. Rahbek O, Kold S, Overgaard S, Søballe K. Light microscopic identification and semi-quantification of polyethylene particles in methylmetacrylate and paraffin embedded experimental bone-implant specimens. *J Microscopy*, 2005;218:225-32
10. Jacobsen S, Sonne-Holm S, Søballe K, Gebuhr P, Lund B. Joint space width in hip dysplasia. A case-control study of eighty-one adult subjects with hip dysplasia followed for a decade. *J Bone Joint Surg Br.* 2005;87:471-7
11. Kold S, Rahbek O, Zippor B, Søballe K. The influence of surface porosity on gap-healing around intra-articular implants in the presence of migrating particles. *Biomaterials*, 2005;26:4728-36
12. Rahbek O, Kold S, Bendix K, Overgaard S, Søballe K. No effect of hydroxyapatite particles in phagocytosable sizes on implant fixation. An experimental study in dogs. *J Biomed Mater Res A*, 2005;73:150-7
13. Kold S, Rahbek O, Toft M, Ding M, Overgaard S, Søballe K. Bone compaction enhances implant fixation in a canine gap model. *Journal of Orthopaedic Research* 2005,23, 824-830
14. Rahbek O, Kold S, Bendix K, Overgaard S, Søballe K. Superior sealing effect of hydroxyapatite coating compared to porous coated implants. Experimental studies on the migration of polyethylene particles around stable and unstable implants in dogs. *Acta Orthopaedica* 2005;76:375-385
15. Koefoed M, Gromov K, Ulrich-Vinther M, Søballe K, Hiromu, Reynolds D, Awad H, Rubery P, Zhang X, O'Keefe R. Biological Effects of rAAV-caAlk2 Coating on Structural Allograft Healing. *Mol Ther.* 2005;12:212-8
16. Rahbek O, Kold S, Zippor B, Overgaard S, Søballe K. Particle migration and gap healing around trabecular metal implants. *Int Orthop.* 2005;29:368-74
17. Laursen MB, Nielsen PT, Søballe K. DXA scanning of acetabulum in patients with cementless total hip arthroplasty. *J Clin Densitom.* 2005;8:476-83
18. Ulrich-Vinther M, Stengaard C, Schwarz E M, Goldring M B, Soballe K. Adeno-Associated Vector mediated gene transfer of Transforming Growth Factor – beta1 to normal and osteoarthritic human chondrocytes stimulates cartilage anabolism. *Eur Cell Mat J*, 2005;10:40-59
19. Elmengaard B, Bechtold JE, Søballe K. In vivo effects of RGD-coated titanium implants inserted in two bone-gap models. *J Biomed Mater Res A* 2005;75:249-55
20. Jacobsen S, Rømer L, Søballe K. Degeneration in dysplastic hips. A Computer Tomography study. *Skeletal Radiology*, 2005;34:778-84
21. Ulrich-Vinther M, Schwarz E M, Pedersen F S, Soballe K, Andreassen T T. Gene therapy with human osteoprotegerin decreases callus remodelling with limited effects on biomechanical properties. *Bone*, 2005;37:751-8
22. Pedersen AB, Johnsen SP, Overgaard S, Søballe K, Sørensen HAT, Lucht U. Regional variation in incidence of primary total hip arthroplasties and revisions in Denmark, 1996-2002. *Acta Orthopaedica* 2005;76:815-822
23. Mechlenburg I, Nyengaard J, Rømer L, Søballe K. Prospective bone density changes after peri-acetabular osteotomy – a methodological study. *Int Orthop*, 2005;29:281-6
24. Kold S, Rahbek O, Zippor B, Bechtold JE, Søballe K. Bone compaction enhances fixation of hydroxyapatite coated implants in a canine gap model. *J Biomed Mater Res B Appl Biomater.* 2005;75:49-55
25. Kold S, Rahbek O, Zippor B, Søballe K. No adverse effects of bone compaction on implant fixation after resorption of compacted bone in dogs. *Acta Orthop* 2005;76:912-9

## 2006

26. Kold S, Rahbek O, Vestermark M, Overgaard S, Soballe K. Bone compaction enhances fixation of weight-bearing hydroxyapatite-coated implants. *J Arthroplasty*. 2006;21:263-70.
27. Jakobsen T, Kold S, Bechtold JE, Elmengaard B, Soballe K. Effect of topical alendronate treatment on fixation of implants inserted with bone compaction. *Clin Orthop Relat Res*. 2006;444:229-34.
28. Pedersen EN, Alkjaer T, Soballe K, Simonsen EB. Walking pattern in 9 women with hip dysplasia 18 months after periacetabular osteotomy. *Acta Orthop*. 2006;77:203-8.
29. Laursen MB, Nielsen PT, Soballe K. Detection of bony defects around cementless acetabular components in total hip arthroplasty: a DEXA study on 10 human cadavers. *Acta Orthop*. 2006;77:209-17.
30. Jacobsen S, Romer L, Soballe K. The other hip in unilateral hip dysplasia. *Clin Orthop Relat Res*. 2006;446:239-46.
31. Toftdahl K, Nikolajsen L, Soballe K, Tonnesen E. Postoperative analgesia following total knee arthroplasty. *Ugeskr Laeger*. 2006;168:1991-6.
32. Petersen MK, Soballe K. Length of stay after total hip and knee arthroplasty. *Ugeskr Laeger*. 2006;168:2137.
33. Nygaard M, Elling F, Bastholm L, Soballe K, Borgwardt A. No difference in early cellular response of the pseudo-synovial membrane after total hip arthroplasty: comparison of 3 combinations of bearing materials. *Acta Orthop*. 2006;77:402-12.
34. Conroy MJ, Pedrono A, Bechtold JE, Soballe K, Ambard D, Swider P. High-resolution magnetic resonance flow imaging in a model of porous bone-implant interface. *Magn Reson Imaging*. 2006;24:657-61.
35. Baad-Hansen T, Kold S, Fledelius W, Nielsen PT, Soballe K. Comparison of performance of conventional and minimally invasive surgery acetabular reamers. *Clin Orthop Relat Res*. 2006;448:173-9.
36. Skott M, Andreassen TT, Ulrich-Vinther M, Chen X, Keyler DE, LeSage MG, Pentel PR, Bechtold JE, Soballe K. Tobacco extract but not nicotine impairs the mechanical strength of fracture healing in rats. *J Orthop Res*. 2006;24:1472-9.
37. Petersen MK, Madsen C, Andersen NT, Soballe K. Efficacy of multimodal optimization of mobilization and nutrition in patients undergoing hip replacement: a randomized clinical trial. *Acta Anaesthesiol Scand*. 2006;50:712-7.
38. Swider P, Mouzin O, Bechtold J, Pedrono A, Søballe K. Biomechanical analysis of the shear behavior adjacent to an axially loaded implant. *J Biomech*. 2006;39:1873-1882.
39. Baas J, Lamberg A, Jensen TB, Elmengaard B, Soballe K. The bovine bone protein lyophilisate Colloss improves fixation of allografted implants - an experimental study in dogs. *Acta Orthop*. 2006;77:791-8.
40. Lamberg A, Schmidmaier G, Soballe K, Elmengaard B. Locally delivered TGF-beta1 and IGF-1 enhance the fixation of titanium implants: a study in dogs. *Acta Orthop*. 2006;77:799-805.
41. Johnsen SP, Sorensen HT, Lucht U, Soballe K, Overgaard S, Pedersen AB. Patient-related predictors of implant failure after primary total hip replacement in the initial, short- and long-terms. A nationwide Danish follow-up study including 36,984 patients. *J Bone Joint Surg Br*. 2006;88:1303-8.

## 2007

42. Jensen TB, Overgaard S, Lind M, Rahbek O, Bunger C, Soballe K. Osteogenic protein-1 increases the fixation of implants grafted with morcellised bone allograft and ProOsteon bone substitute: an experimental study in dogs. *J Bone Joint Surg Br*. 2007;89:121-6.
43. Swider P, Conroy M, Pedrono A, Ambard D, Mantell S, Soballe K, Bechtold JE. Use of high-resolution MRI for investigation of fluid flow and global permeability in a material with interconnected porosity. *J Biomech*. 2007;40:2112-8.
44. Troelsen A, Soballe K. Idiopathic osteoarthritis of the hip. *Ugeskr Laeger*. 2007;169:390. Danish. No abstract available.
45. Troelsen A, Romer L, Soballe K. Hip dysplasia: clinical assessment, radiologic evaluation and reference. *Ugeskr Laeger*. 2007;169:394-6. Danish.

46. Petersen MK, Andersen KV, Andersen NT, Soballe K. "To whom do the results of this trial apply?" External validity of a randomized controlled trial involving 130 patients scheduled for primary total hip replacement. *Acta Orthop.* 2007;78:12-8.
47. Mechlenburg I, Nyengaard JR, Gelineck J, Soballe K. Cartilage thickness in the hip joint measured by MRI and stereology — a methodological study. *Osteoarthritis Cartilage.* 2007;15:366-71.
48. Jakobsen T, Kold S, Bechtold JE, Elmengaard B, Soballe K. Local alendronate increases fixation of implants inserted with bone compaction: 12-week canine study. *J Orthop Res.* 2007;25:432-41.
49. Laursen MB, Nielsen PT, Soballe K. Bone remodelling around HA-coated acetabular cups: a DEXA study with a 3-year follow-up in a randomised trial. *Int Orthop.* 2007;31:199-204.
50. Toftdahl K, Nikolajsen L, Haraldsted V, Madsen F, Tonnesen EK, Soballe K. Comparison of peri- and intraarticular analgesia with femoral nerve block after total knee arthroplasty: a randomized clinical trial. *Acta Orthop.* 2007;78:172-9.
51. Andersen KV, Pfeiffer-Jensen M, Haraldsted V, Soballe K. Reduced hospital stay and narcotic consumption, and improved mobilization with local and intraarticular infiltration after hip arthroplasty: a randomized clinical trial of an intraarticular technique versus epidural infusion in 80 patients. *Acta Orthop.* 2007;78:180-6.
52. Stender S, Murphy M, O'Brien T, Stengaard C, Ulrich-Vinther M, Soballe K, Barry F. Adeno-associated viral vector transduction of human mesenchymal stem cells. *Eur Cell Mater.* 2007 31;13:93-9; discussion 99.
53. Jensen TB, Bechtold JE, Chen X, Soballe K. Systemic alendronate treatment improves fixation of press-fit implants: a canine study using nonloaded implants. *J Orthop Res.* 2007;25:772-8.
54. Mechlenburg I, Kold S, Romer L, Soballe K. Safe fixation with two acetabular screws after Ganz peri-acetabular osteotomy. *Acta Orthop.* 2007;78:344-9.
55. Jakobsen T, Baas J, Bechtold JE, Elmengaard B, Soballe K. Soaking Morselized Allograft in Bisphosphonate Can Impair Implant Fixation. *Clin Orthop Relat Res.* 2007;463:195-201.
56. Jakobsen SS, Larsen A, Stoltenberg M, Bruun JM, Soballe K. Effects of as-cast and wrought Cobalt-Chrome-Molybdenum and Titanium-Aluminium-Vanadium alloys on cytokine gene expression and protein secretion in J774A.1 macrophages. *Eur Cell Mater.* 2007;14:45-54; discussion 54-5.
57. Troelsen A, Jacobsen S, Bolvig L, Gelineck J, Rømer L, Søballe K. Ultrasound versus magnetic resonance arthrography in acetabular labral tear diagnostics: a prospective comparison in 20 dysplastic hips. *Acta Radiol.* 2007;48:1004-10.
58. Baad-Hansen T, Kold S, Kaptein BL, Søballe K. High-precision measurements of cementless acetabular components using model-based RSA: an experimental study. *Acta Orthop.* 2007;78:463-9.
59. Jørgensen PH, Gromov K, Søballe K. Prevention of prosthesis infections. *Ugeskr Laeger.* 2007; 169:4159-63. Review. Danish.
60. Jakobsen SS, Danscher G, Stoltenberg M, Larsen A, Bruun JM, Mygind T, Kemp K, Soballe K. Cobalt-chromium-molybdenum alloy causes metal accumulation and metallothionein up-regulation in rat liver and kidney. *Basic Clin Pharmacol Toxicol.* 2007;101:441-6.
61. Søballe K, Chen X, Jensen TB, Kidder L, Bechtold JE. Alendronate treatment in the revision setting, with and without controlled implant motion: an experimental study in dogs. *Acta Orthop.* 2007;78:800-7.

## 2008

62. Li D, Gromov K, Søballe K, Puzas JE, O'Keefe RJ, Awad H, Drissi H, Schwarz EM. Quantitative mouse model of implant-associated osteomyelitis and the kinetics of microbial growth, osteolysis, and humoral immunity. *J Orthop Res.* 2008;26:96-105.
63. Troelsen A, Elmengaard B, Søballe K. A new minimally invasive transartorial approach for peri-acetabular osteotomy. *J Bone Joint Surg Am.* 2008;90:493-8.
64. Basile P, Dadali T, Jacobson J, Hasslund S, Ulrich-Vinther M, Søballe K, Nishio Y, Drissi MH, Langstein HN, Mitten DJ, O'Keefe RJ, Schwarz EM, Awad HA. Freeze-dried tendon allografts as tissue-engineering scaffolds for Gdf5 gene delivery. *Mol Ther.* 2008;16:466-73.
65. Troelsen A, Jacobsen S, Rømer L, Søballe K. Weightbearing Anteroposterior Pelvic Radiographs are Recommended in DDH Assessment. *Clin Orthop Relat Res.* 2008;466:813-9.

66. Troelsen A, Elmengaard B, Rømer L, Søballe K. Reliable angle assessment during periacetabular osteotomy with a novel device. *Clin Orthop Relat Res.* 2008;466:1169-76.
67. Thillemann TM, Pedersen AB, Johnsen SP, Søballe K, Increased Risk of Inferior Outcomes after Intraoperative Femoral Fracture in Primary Total Hip Arthroplasty. *Acta Orthopaedica*, Accepted for publication oktober 2007
68. Thillemann TM, Pedersen AB, Johnsen SP, Søballe K, Implant Survival after Primary Total Hip Arthroplasty due to Childhood hip disorders: Results from the Danish Hip Arthroplasty Register. *Acta Orthopaedica*, Accepted for publication january 2008
69. Daugaard H, Elmengaard B, Bechtold JE, Soballe K. Bone growth enhancement in vivo on press-fit titanium alloy implants with acid etched microtexture. *J Biomed Mater Res A.* 2008 Jan 9; [Epub ahead of print]
70. Hasslund S, Jacobson JA, Dadali T, Basile P, Ulrich-Vinther M, Søballe K, Schwarz EM, O'Keefe RJ, Mitten DJ, Awad HA. Adhesions in a murine flexor tendon graft model: Autograft versus allograft reconstruction. *J Orthop Res.* 2008 Jan 9; [Epub ahead of print]
71. Zainali K, Danscher G, Jakobsen T, Jakobsen SS, Baas J, Møller P, Bechtold JE, Soballe K. Effects of gold coating on experimental implant fixation. *J Biomed Mater Res A.* 2008 Mar 11; [Epub ahead of print]
72. Baas J, Elmengaard B, Jensen TB, Jakobsen T, Andersen NT, Soballe K. The effect of pretreating morselized allograft bone with rhBMP-2 and/or pamidronate on the fixation of porous Ti and HA-coated implants. *Biomaterials.* 2008 Apr 11; [Epub ahead of print]
73. Baas J, Elmengaard B, Bechtold J, Chen X, Soballe K. Ceramic bone graft substitute with equine bone protein extract is comparable to allograft in terms of implant fixation—a study in dogs. *Acta Orthopaedica* accepted
74. Baas J. Adjuvant therapies of bone graft around non-cemented experimental orthopaedic implants - stereological methods and experiments in dogs. Thesis. *Acta Orthopaedica (Suppl 329)* 2008; 79 accepted
75. 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 arthroplasty. *BMC.* (in press)
76. Larsen K, Hansen TB, Søballe K. Hip arthroplasty patients benefit after accelerated perioperative care and rehabilitation intervention. *Acta Orthop Scand.* (in press)
77. Larsen K, Hansen TB, Thomsen PB, Christiansen T, Søballe K. Cost-efficacy of Accelerated Perioperative Care and Rehabilitation Intervention After Total Hip and Knee Arthroplasty. *J Bone Joint Surg Am.* (in press)
78. Larsen K, Sørensen OG, Hansen TB, Thomsen PB, Søballe K. Accelerated perioperative care and rehabilitation intervention for hip and knee replacement is effective! *Acta Orthop Scand.* (in press)

## Appendix 2: CV for Senior Researchers

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### Personal data

**Name:** Lars Simon Rasmussen  
**Date of birth:** 6<sup>th</sup> October 1959  
**Private address:** Amalie Skrams Alle 5, DK-2500 Valby  
**Work address:** Department of Anaesthesia, Section 4231, Centre of Head and Orthopaedics, Copenhagen University Hospital, Rigshospitalet, Blegdamsvej 9, DK-2100 Copenhagen  
**Telephone:** +4536454828 (private) / +4535453488 (office)  
**E-mail:** [lsr@rh.dk](mailto:lsr@rh.dk)

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### Education

1985: Medical Doctor, University of Copenhagen  
1994: Accredited specialist in Anaesthesia and Intensive Care  
1996: European Diploma in Anaesthesia and Intensive Care  
1999: Ph.D. dissertation: Postoperative Cognitive Dysfunction in Elderly Patients  
2007: Medical Doctoral Thesis: Postoperative cognitive dysfunction - incidence, risk factors, and correlation with biochemical markers for brain damage

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### Scientific positions

1994-1997: PhD student at University of Copenhagen  
2001- Clinical lecturer in anaesthesia at University of Copenhagen  
2002- Member of Editorial Board for Acta Anaesthesiologica Scandinavica

Reviewer for Lancet, Stroke, Circulation, Anesthesiology, Anesthesia and Analgesia, British Journal of Anaesthesia, Acta Anaesthesiologica Scandinavica, European Journal of Anaesthesiology, Neurotoxicity Research, Acta Neurologica Scandinavica, Journal of Clinical and Experimental Neuropsychology, European Journal of Vascular and Endovascular Surgery, Drugs and Aging, BMC Neurology, Clinical Chemistry and Laboratory Medicine

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### Bibliography

Peer-reviewed papers: 74  
Abstracts and proceedings: 32  
Invited lectures: 58  
Book chapters: 5  
Editor of 2 teaching books

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### Supervisor Experience

Diploma projects: 18  
PhD projects: 3 completed  
PhD projects: 4 in progress

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### Member of evaluation of scientific theses

|                 |   |
|-----------------|---|
| PhD theses:     | 1 |
| Diploma theses: | 2 |

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### Current research interest

Postoperative cognitive dysfunction, postoperative delirium, resuscitation, airway management, trauma care

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### List of publications (last 3 years)

1. Holm-Knudsen R, Eriksen K, Rasmussen LS. Using a nasopharyngeal airway during fiberoptic intubation in small children with a difficult airway. *Paediatr Anaesth* 2005; 15: 839-45
2. Vedtofte JI, Rasmussen LS, Jørgensen S. Faste og tørst før ortopædkirurgisk sårrevision. *Ugeskr Læger* 2005; 167: 1290-3
3. Stoevring B, Jaliashvili I, Thougard AV, Ensinger C, Høgdall CK, Rasmussen LS, Sellebjerg F, Christiansen M. Tetraacetin in Cerebrospinal Fluid: Biochemical characterisation and evidence of intrathecal synthesis or selective up-take into CSF. *Clin Chim Acta* 2005; 359: 65-71
4. Rosenstock C, Gillesberg I, Gätke MR, Levin D, Kristensen MS, Rasmussen LS. Inter-observer agreement of tests used for prediction of difficult laryngoscopy/tracheal intubation. *Acta Anaesthesiol Scand* 2005; 49:1057-62
5. Rasmussen LS, O'Brien JT, Silverstein JH, Johnson TW, Siersma VD, Canet J, Jolles J, Hanning CD, Kuipers HM, Abildstrom H, Papaioannou A, Raeder J, Yli-Hankala A, Sneyd JR, Munoz L, Moller JT, for the ISPOCD2 investigators Is Perioperative Cortisol Secretion related to Postoperative Cognitive Dysfunction? *Acta Anaesthesiol Scand* 2005; 49: 1225-31
6. Hesselheldt R, Kristensen MS, Rasmussen LS. Evaluation of the airway of the SimMan™ full-scale patient-simulator. *Acta Anaesthesiol Scand* 2005; 49: 1339-45
7. Meyhoff CS, Thomsen CH, Rasmussen LS, Nielsen PR. High incidence of chronic pain following surgery for pelvic fracture. *Clin J Pain* 2006; 22: 167-72
8. Horsted TI, Wanscher M, Rasmussen LS, Lippert FK, Kjærgaard J, Hassager C. Hypotermibehandling efter hjertestop – en status. *Ugeskr Læger* 2006 30;168:458-61
9. Isbye DL, Rasmussen LS, Lippert FK, Rudolph SF, Ringsted CV. Laypersons may learn basic life support in 24 min using a personal resuscitation manikin. *Resuscitation* 2006; 69: 435-42
10. Rosenstock C, Hansen EG, Kristensen MS, Rasmussen LS, Skak C, Østergaard D. Qualitative Analysis of Unanticipated Difficult Airway Management. *Acta Anaesthesiol Scand* 2006; 50: 290-7
11. Steinmetz J, Rasmussen LS, Nielsen SL. Long-term prognosis for patients with chronic obstructive pulmonary disease treated in the prehospital setting – is it influenced by hospital admission? *Chest* 2006; 130:676-80
12. Walther-Larsen S, Rasmussen LS. The former preterm infant and risk of postoperative apnoea- Recommendations for management. *Acta Anaesthesiol Scand* 2006; 50: 888-93
13. Rasmussen LS, Schmehl W, Jakobsson J. Comparison of xenon with propofol for supplementary general anaesthesia for knee replacement: a randomised study. *Br J Anaesth* 2006; 97: 154-9
14. Østergaard Jensen B, Hughes P, Rasmussen LS, Pedersen PU, Steinbrüchel D. Cognitive outcomes in elderly high-risk patients after off-pump versus conventional coronary artery bypass grafting. *Circulation* 2006; 113: 2790-5
15. Østergaard Jensen B, Hughes P, Rasmussen LS, Pedersen PU, Steinbrüchel D. Health related quality of life following off-pump versus on-pump coronary artery bypass grafting in elderly moderate to high-risk patients: a randomized trial. *Eur J Cardiothorac Surg* 2006; 30: 294-9
16. Rasmussen LS. Postoperative cognitive dysfunction: Incidence and prevention. *Best Pract Res Clin Anaesthesiology* 2006; 20: 315-30.
17. Stoevring B, Jaliashvili I, Thougard AV, Ensinger C, Høgdall CK, Rasmussen LS, Sellebjerg F, Christiansen M. Tetraacetin in cerebrospinal fluid of patients with multiple sclerosis. *Scand J Clin Lab Invest.* 2006; 66: 577-84.

18. Steinmetz J, Nielsen SL, Rasmussen LS. Langtidsprognosen for kronisk obstruktivt lungesygge efter præhospitalet behandling af H:S Lægeambulance. *Scand J Trauma Resusc Emerg Med* 2006;14:182-5. Parallellpublikation.
19. Jensen BO, Hughest P, Rasmussen LS, Pedersen PU, Steinbruchel DA Kognitive funktioner hos ældre patienter i højrisiko-gruppe efter koronararteriebypassoperation uden anvendelse af hjerte-lunge-maskine versus konventionel bypassoperation - et randomiseret studie – sekundærpublikation. *Ugeskr Læger* 2006; 168: 3820-3822.
20. Silverstein JH, Steinmetz J, Reichenberg A, Harvey PD, Rasmussen LS. Postoperative Cognitive Dysfunction in Patients with Preoperative Cognitive Impairment: Which Domains Are Most Vulnerable? *Anesthesiology* 2007; 106: 431-5
21. Horsted TI, Rasmussen LS, Meyhoff CS, Nielsen SL. Long-term prognosis after out-of-hospital cardiac arrest. *Resuscitation* 2007; 72: 214-8
22. Steinmetz J, Holm-Knudsen R, Sørensen MK, Eriksen K, Rasmussen LS. Hemodynamic differences between propofol-remifentanil and sevoflurane anesthesia for repair of cleft lip and palate in infants. *Paediatr Anaesth* 2007; 17: 32-7
23. Isbye DL, Meyhoff CS, Lippert FK, Rasmussen LS. Skill retention in adults and in children three months after basic life support training using a simple personal resuscitation manikin. *Resuscitation* 2007; 74: 296-302
24. Steinmetz J, Holm-Knudsen R, Eriksen K, Marxen D, Rasmussen LS. Quality differences in postoperative sleep between propofol-remifentanil and sevoflurane anesthesia in infants. *Anesth Analg* 2007; 104: 779-83
25. Nielsen PR, Nørgaard L, Rasmussen LS, Kehlet H. Prediction of postoperative pain by an electrical pain stimulus. *Acta Anaesthesiol Scand* 2007; 51: 582-6
26. Rudolph JL, Jones RN, Rasmussen LS, Silverstein JH, Inouye SK, Marcantonio ER. Independent vascular and cognitive risk factors for postoperative delirium. *Am J Med* 2007; 120: 807-13
27. Andersen LØ, Isbye DL, Rasmussen LS. Increasing compression depth during manikin CPR using a simple backboard. *Acta Anaesthesiol Scand* 2007; 51: 747-50
28. Meyhoff CS, Hesselbjerg L, Koscielniak-Nielsen Z, Rasmussen LS. Biphasic cardiac output changes during onset of spinal anaesthesia in elderly patients. *Eur J Anaesthesiol* 2007; 24: 770-5
29. Holler NG, Mantoni T, Nielsen SL, Lippert F, Rasmussen LS. Long-Term survival after Out-Of-Hospital Cardiac Arrest. *Resuscitation* 2007; 75: 23-8
30. Gögenur, I, Middleton, B, Burgdorf, S, Rasmussen, LS, Skene DJ, Rosenberg J. Impact of sleep and circadian disturbances in urinary 6-sulfatoxymelatonin levels on cognitive function after major surgery. *J Pineal Res* 2007; 43: 179-84
31. Vedtofte JI, Rasmussen LS. The use of bispectral index monitoring in education - A tool to improve anaesthesia practice. *J Adv Nurs* 2007; 59: 577-82
32. Mathiesen O, Nielsen SL, Rasmussen LS. Hvordan alarmeres præhospitalet hjertestop? *Ugeskr Læger* 2008; 170: 1145-7
33. Isbye DL, Rasmussen LS, Ringsted C, Lippert FL. Disseminating CPR training by distributing 35.000 personal manikins among school children. *Circulation* 2007; 116:1380-5
34. Stensballe J, Tvede M, Looms D, Lippert FK, Dahl B, Tønnesen E, Rasmussen LS. Infection risk with nitrofurazone-impregnated urinary catheters in trauma patients. A randomized trial. *Ann Int Med* 2007; 147: 285-93
35. Steinmetz J, Rasmussen LS and the ISPOCD group. Choice reaction time in patients with Postoperative Cognitive Dysfunction. *Acta Anaesthesiol Scand* 2008; 52: 95-8
36. Steinmetz J, Barnung S, Nielsen SL, Risom M, Rasmussen LS. Improved survival after out-of-hospital cardiac arrest using new guidelines. *Acta Anaesthesiol Scand* 2008 (in press)
37. Rudolph JL, Marcantonio ER, Culley DJ, Silverstein JH, Rasmussen LS, Crosby GJ, Inouye SK. Delirium is associated with early postoperative cognitive dysfunction. *Anaesthesia* 2008 (in press)
38. Fischer CE, Barnung S, Nielsen SL, Rasmussen LS. Prehospital identification of stroke – room for improvement. *Eur J Neurol* 2008 (in press)



## Editorials

1. Rasmussen LS, Viby-Mogensen J. Rapid sequence intubation - how? *Acta Anaesthesiol Scand*. 2007; 51: 787-8.
2. Rasmussen LS. Anaesthesia and amnesia. *Acta Anaesthesiol Scand* 2007; 51: 966-7.
3. Rasmussen LS. Focus on: Acute Pain. *Curr Anaesth Crit Care* 2007; 18: 125
4. Rasmussen LS, Gisvold SE. New author guidelines *Acta Anaesthesiol Scand* 2008 (in press)

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### Personal data

Name: **Michael Rud Lassen**  
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Private address: Skovgrænsen 6, DK-2960 Rungsted Kyst  
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### Education

1982: MD, University of Copenhagen, Denmark

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### Scientific positions

1982: Copenhagen Municipal Hospital  
1982-1985: Registrar at Medical Dept. 3, Aalborg Hospital  
1985-1994: Depts. of Orthopedics, Aalborg Hospital  
1994-1995: Spine Section, University Hospital of Aarhus  
1995-1996: Dept. of Orthopedics, Odense University Hospital  
1996-2002: Dept. of Orthopedics, Hillerød Central Hospital  
2002- Consultant Surgeon, Clinic for Spine Surgery and Chairman of Clinical Trial Unit Hørsholm Hospital

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### Bibliography

Peer-reviewed papers: 82  
Abstracts and proceedings: >100  
Invited lectures: 3  
Book chapters: 3  
Book chapters in teaching books: 2

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### Supervisor Experience

PhD projects: 2

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### Current research interest

Spine surgery, bone grafting, tissue engineering, pathophysiology, coagulation, anticoagulant drug, diagnostics, immune response research, clinical trials, vaccines, growth factors, cartilage growth, pharmacoeconomics, clinical studies in non-fusion techniques in degenerative disc disease.

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### Awards

Best oral Award, Dansk Ortopædisk selskabs annual meeting Copenhagen 1995

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### Main publications

1. Bauer KA, Eriksson BI, Lassen MR, Turpie AG; Steering Committee of the Pentasaccharide in Major Knee Surgery Study. Fondaparinux compared with enoxaparin for the prevention of venous thromboembolism after elective major knee surgery. *N Engl J Med.* 2001;345:1305-10.

2. Eriksson BI, Bauer KA, Lassen MR, Turpie AG; Steering Committee of the Pentasaccharide in Hip-Fracture Surgery Study. Fondaparinux compared with enoxaparin for the prevention of venous thromboembolism after hip-fracture surgery. *N Engl J Med.* 2001; 345:1298-304.
3. Turpie AG, Bauer KA, Eriksson BI, Lassen MR; PENTATHALON 2000 Study Steering Committee. Postoperative fondaparinux versus postoperative enoxaparin for prevention of venous thromboembolism after elective hip-replacement surgery: a randomised double-blind trial. *Lancet.* 2002;359:1721-6.
4. Lassen MR, Bauer KA, Eriksson BI, Turpie AG; European Pentasaccharide Elective Surgery Study (EPHESUS) Steering Committee. Postoperative fondaparinux versus preoperative enoxaparin for prevention of venous thromboembolism in elective hip-replacement surgery: a randomised double-blind comparison. *Lancet.* 2002;359:1715-20.
5. Lassen MR, Borris LC, Nakov RL. Use of the low-molecular-weight heparin reviparin to prevent deep-vein thrombosis after leg injury requiring immobilization. *N Engl J Med* 2002;347:726-30
6. Geerts W, Ray JG, Colwell CW, Bergqvist D, Pineo GF, Lassen MR, Heit JA Prevention of Venous Thromboembolism. 7<sup>th</sup> ACCP Guidelines. *Chest.* 2005;128:3775-3776.
7. Cohen AT, Davidson BL, Gallus AS, Lassen MR, Prins MH, Tomkowski W, Turpie AG, Egberts JF, Lensing AW; ARTEMIS Investigators. Efficacy and safety of fondaparinux for the prevention of venous thromboembolism in older acute medical patients: randomised placebo controlled trial. *BMJ* 2006; 332: 325-9.
8. Colwell CW Jr, Lassen MR, Bergqvist D, Geerts WH, Pineo GF, Heit JA, Ray JG. Prophylaxis for the thromboembolic disease—recommendations from the American College of Chest Physicians—are they appropriate for orthopaedic surgery? *J Arthroplasty* 2006; 21: 148-9.
9. Lassen MR, Solgaard S, Kjærsgaard AG, Olsen C, Lind B, Mittet K, Coff-Ganes H. A Pilot study of the effects of Vivostat patient-derived fibrin sealant in reducing blood loss in primary hip arthroplasty. *Clin Appl Thromb Hemost* 2006;12:352-7
10. Lassen MR, Davidson BL, Gallus A, Pineo G, Ansell J, Deitchman D. The efficacy and safety of apixaban, an oral, direct factor Xa inhibitor, as thromboprophylaxis in patients following total knee replacement. *J Thromb Haemost.* 2007;5:2368-75.
11. Eriksson BI, Turpie AG, Lassen MR, Prins MH, Agnelli G, Kälebo P, Gaillard ML, Meems L; ONYX study group. A dose escalation study of YM150, an oral direct factor Xa inhibitor, in the prevention of venous thromboembolism in elective primary hip replacement surgery. *J Thromb Haemost.* 2007 5:1660-5.
12. Borris LC, Breindahl M, Ryge C, Sommer HM, Lassen MR; The uF1+2 study group. Prothrombin fragment 1+2 in urine as an indicator of sustained coagulation activation after total hip arthroplasty. *Thromb Res.* 2007;121:369-76.
13. Dahl OE, Borris LC, Bergqvist D, Schnack Rasmussen M, Eriksson BI, Kakkar AK, Colwell CW, Caprini JA, Fletcher J, Friedman RJ, Lassen MR, Frostick SP, Sakon M, Kwong LM, Kakkar VV. Major joint replacement. A model for antithrombotic drug development: from proof-of-concept to clinical use. *Int Angiol.* 2008;27:60-7.
14. Eriksson BI, Dahl OE, Lassen MR, Ward DP, Rothlein R, Davis G, Turpie AG; Fixit Study Group. Partial factor IXa inhibition with TTP889 for prevention of venous thromboembolism: an exploratory study. *J Thromb Haemost.* 2008;6:457-63.

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### Personal data

Name: **Henrik Husted**  
Date of birth: 23<sup>rd</sup> October 1964  
Private address: Rådhusvej 27, DK-2920 Charlottenlund  
Work address: Dep. of Orthopedics, Hvidovre University Hospital, Kettegaard Alle 30, DK-2650 Hvidovre  
Telephone: +4536326037  
E-mail: [henrikhusted@dadlnet.dk](mailto:henrikhusted@dadlnet.dk)

---

### Education

1991: cand. med., Odense University.  
2000: specialist in orthopaedics  
2003: consultant & head of arthroplasty section, Hvidovre University Hospital, Denmark

---

### Scientific positions

1991: MD

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### Bibliography

Peer-reviewed papers: 37  
Abstracts and proceedings: 25  
Invited lectures: 8  
Book chapters: 3  
Book chapters in teaching books: 1

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### Supervisor Experience

multiple for interns and specialists

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### Selection Committee

joined the National Board of Health as a specialist  
reviewer for the danish medical journal  
member of the board, Danish Society for Hip and Knee Surgery

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### Current research interest

ongoing research (research group: pain treatment/LIA, mobilization, logistics, THA, TKA, revision, infection, new materials and techniques in lower joint replacements)  
developed accelerated track + ongoing evaluation & optimization (ANORAK-HH)  
co-writer of national reference programmes for hip and knee replacement surgery

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### List of publications (last 3 years)

1. Husted H, Holm G, Sonne-Holm S. Accelereret forløb: høj tilfredshed og 4 dages indlæggelse ved hofte- og knæalloplastik på uselekterede patienter. Ugeskrift for Læger 2005;167:2043-8.
2. Palm H, Husted H. Voluntary dislocation of a total hip arthroplasty with a constrained acetabular component – a case report. Acta Orthopaedica Scandinavica 2005;76:602-3

3. Husted H, Toftgaard Jensen T. Application of tourniquets on flexed knees does not decrease the number of lateral release needed. A prospective randomised study in 100 patients. *J Arthroplasty* 2005;20:694-7.
4. Husted H, Holm G, Rud K, Bach-Dal C, Hansen HC, Andersen KL, Kehlet H. Indlæggelsesvarighed ved primær total hofte- og knæalloplastik i Danmark 2001-2003. *Ugeskrift for Læger* 2006;168:276-9
5. Krogsgaard MR, Jensen PK, Kjær I, Husted H, Lorentzen J, Hvass-Christensen B, Bach Christensen S, Larsen K, Sonne-Holm S. Increasing incidence of club foot with higher population density. Incidences and geographical variation of inborn foot deformities in Denmark during a 16-year period – an epidemiological study of 936,525 births. *Acta Orthopaedica Scandinavica* 2006;77:839-46.
6. Husted H, Hansen HC, Holm G, Bach-Dal C, Rud K, Andersen KL, Kehlet H. Indlæggelsesvarighed efter operation med hofte- og knæalloplastik i Danmark (I): Volumen, morbiditet, mortalitet og resourceforbrug. En landsdækkende undersøgelse på ortopædkirurgiske afdelinger i Danmark. *Ugeskrift for Læger* 2006;168:2139-43.
7. Husted H, Hansen HC, Holm G, Bach-Dal C, Rud K, Andersen KL, Kehlet H. Kort vs. lang hospitalisering efter hofte- og knæalloplastik (II): Organisatoriske og faglige forskelle. *Ugeskrift for Læger* 2006;168:2144-8.
8. Husted H, Hansen HC, Holm G, Bach-Dal C, Rud K, Andersen KL, Kehlet H. Patienttilfredshed efter hofte- og knæalloplastik med kort vs. lang indlæggelse (III). *Ugeskrift for Læger* 2006;168:2148-51.
9. Husted H, Holm G. Fast track in total hip and knee arthroplasty – experiences from Hvidovre University Hospital, Denmark. *Injury* 2006;37(suppl 5):31-5
10. Holte K, Kristensen BB, Valentiner L, Foss NB, Husted H, Kehlet H. Liberal versus restrictive fluid management in knee arthroplasty: a randomized, double-blind study. *Anesth Analg* 2007;105:465-74.
11. Husted H, Holm G, Jacobsen S. Accelerated tracks in total hip and knee replacement – what matters? *Acta Orthop* 2008, in press
12. Andersen LØ, Husted H, Otte KS, Kristensen BB, Kehlet H. High-volume infiltration analgesia in total knee arthroplasty. A randomized, double-blind, placebo-controlled trial. *Br J Anaesth* 2008 submitted
13. Andersen LØ, Husted H, Otte KS, Kristensen BB, Kehlet H. Local anesthetics after total knee arthroplasty: intra- vs. extraarticular administration? A randomized, double-blind, placebo-controlled study. *Acta Orthopaedica* 2008, in press
14. Andersen LØ, Husted H, Otte KS, Kristensen BB, Kehlet H. A compression bandage prolongs duration of local infiltration analgesia in total knee arthroplasty. *Acta Orthopaedica* 2008, submitted
15. Otte KS, Husted H, Andersen LØ, Kristensen BB, Kehlet H. Local infiltration analgesia in total knee arthroplasty and hip resurfacing. A methodological study. *J Arthroplasty* 2008, submitted.
16. Husted H, Hansen HC, Holm G, Bach-Dal C, Rud K, Andersen KL, Kehlet H. What determines length of stay after THA and TKA? a nationwide study in Denmark. *Acta Orthopaedica* 2008, submitted.

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### Personal data

Name: **Pär I. Johansson**  
Date of birth: 10<sup>th</sup> June 1961  
Private address: Bokvägen 9, SE 24471 Dösjebro, Sweden  
Work address : Blood bank, Rigshospitalet, Blegdamsvej 9, DK-2100 Copenhagen  
Telephone: +4535452030  
E-mail: [per.Johansson@rh.regionh.dk](mailto:per.Johansson@rh.regionh.dk)

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### Education

1985-1991 Medical School, University of Lund, Sweden  
1994-1998 Resident in Anaesthesiology, University hospital in Lund, Sweden  
1999-2004 Resident in Clinical Immunology, Rigshospitalet, Copenhagen, Denmark  
2002-2004 Master of Public Administration, Copenhagen Business School, Denmark

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### Scientific positions

1998-1999 Consultant, Dept. of Anaesthesiology, Central Hospital, Kristianstad, Sweden  
2004-2006 Consultant, Dept. of Clinical Immunology, Rigshospitalet, Copenhagen, Denmark  
2006-2007 Medical Director, Transfusion Service, Blood bank, Rigshospitalet, Denmark  
2007- Medical Director, Transfusion Service, Capital Region in Denmark

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### Bibliography

Peer-reviewed papers: >25  
Abstracts and proceedings: >40  
Invited lectures: >50  
Book chapters: 1  
Book chapters in teaching books: 1

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### Supervisor Experience

Diploma projects: 5  
PhD projects: 4 (co-supervisor)

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### Member of evaluation of scientific theses

Diploma theses: 3

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### Current research interest

Basic and clinical research in haemostasis and transfusion medicine. Basic and clinical research in hypercoagulability in Intensive Care, Cancer, Stroke and Trauma. Experimental research in translational oncology focusing on inflammation and haemostasis. Alterations in cancer.

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### Awards

Best lecture Danish Society of Anaesthesiologists 2005

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### List of publications (last 3 years)

1. Simonsen AC, Johansson PI, Flament J et al.. Clinical Efficacy And Safety In Thrombocytopenic Patients Of INTERCEPT Platelets Stored For 7 Days: Results Of A Pilot Feasibility Study. *Transfusion*. 2006;46:424-33.
2. Davids M, Andersen NEO, Johansson PI, Andersen LW. Use of thrombelastography (TEG) and rFVIIa (NovoSeven®) in a paediatric cardiac surgical patient on extra corporeal membrane oxygenation. *J Extra Corp Tech*. 2006;38:165-7.
3. Johansson PI, Eriksen K, Alsbjörn B. Rescue treatment with rFVIIa in patients with life-threatening bleeding secondary to major burn surgery? *J Trauma*. 2006;61:1016-8.
4. Johansson PI, Eriksen K, Alsbjörn B. Major burn surgery – a place for recombinant factor VIIa? *TATM* 2006;8:43-46.
5. Heslet L, Dalsgaard Nielsen J, Levi M, Sengeløv H, Johansson PI. Successful pulmonary administration of activated recombinant factor VII in diffuse alveolar hemorrhage (DAH). *Crit Care*. 2006;21;10:R177
6. Johansson PI. Cost effectiveness of rFVIIa in major burn surgery. *ICU-Management* 2006;6:10-11.
7. Wiinberg B, Røjkjær R, Jensen AL, Johansson PI, Kristensen AT. Study on biological variation of hemostatic parameters in clinically healthy dogs. *Vet J* 2007;174:62-8
8. Bochsén L, Wiinberg B, Kjeldgaard-Hansen M, Steinbruchel D, Johansson PI. In vitro evaluation of the TEG® platelet mapping™ assay in healthy blood donors. *Thrombosis J* 2007 20;5:3.
9. Johansson PI, Stensballe J, Rosenberg I et al. Proactive administration of platelets and plasma for patients with a ruptured abdominal aortic aneurysm: evaluating a change in transfusion practice. *Transfusion* 2007;47:593-8.
10. Johansson PI, Eriksen K, Alsbjörn B. Recombinant FVIIa decreases peri –and postoperative blood transfusion requirement in burn patients undergoing excision and skin grafting. *Burns* 2007 Mar 21; [Epub ahead of print].
11. Bochsén L, Byback-Hansen A, Steinbruchel D, Johansson PI. Platelet reactivity is higher in patients undergoing CABG surgery as compared to healthy blood donors. *Scand Eurovasc J*. 2007;41:321-4.
12. Johansson PI. The Blood Bank: From Provider to Partner in Treatment of Massively Bleeding Patients. *Transfusion*. 2007;47:2:176S-181S;
13. Johansson PI. Treatment of Massively Bleeding Patients: Introducing Real Time Monitoring, Transfusion Packages and Thrombelastography (TEG®). *ISBT Science Series*.2007;1:159–167
14. Svendsen MS, Røjkjær R, Kristensen AT, Salado-Jimena JA, Kjalke M, Johansson PI. Impairment of the hemostatic potential of platelets during storage as evaluated by flow cytometry, thrombin generation, and thrombelastography under conditions promoting formation of coated platelets. *Transfusion*. 2007;47:2057-65.
15. Johansson PI, Bochsén L, Svendsen M, Salado J, Kristensen AT. Investigation of the thrombin generating capacity, evaluated by Thrombogram and clot formation evaluated by Thrombelastography of platelets stored in the blood bank for up to 7 days. *Vox Sang*. 2008;9:113-8.
16. Johansson PI, Ullum H, Secher NH. A retrospective cohort study of blood haemoglobin levels in blood donors and competitive rowers. *Scand J Med Sci Sports*. 2008 Feb 21; [Epub ahead of print]
17. Wiinberg B, Jensen A, Johansson PI, Rozanski E, Tranholm M, Kristensen AT The use of Thrombelastography to evaluate overall hemostatic function in dogs with Disseminated Intravascular Coagulation. *J Vet Intern Med*. 2008;22:357-65
18. Kirkeby A, Torup L, Bochsén L, Kjalke M, Abel K, Theilgaard-Monch K, Johansson PI, Bjørn SE, Gerwien J, Leist M. High-dose erythropoietin alters platelet reactivity and bleeding time in rodents in contrast to the neuroprotective variant carbamyl-erythropoietin (CEPO). *Thromb Haemost*. 2008;99:720-8.
19. Johansson PI, Bochsén L, Stensballe J et al. The effect of a transfusion package on clot formation and stability evaluated by TEG in massively bleeding patients, *Transf Apher Sci*. In press.
20. Johansson PI. Off-label use of recombinant factor VIIa for treatment of haemorrhage: results from randomised clinical trials. *Vox Sang*. In press.
21. Viuff D, Lauritzen B, Pusateri AE, Andersen S, Røjkjær R, Johansson PI. Effect of Hemodilution, Acidosis, and Hypothermia on the Activity of Recombinant Factor VIIa (NovoSeven). *Br J Anaesth* 2008. In press.

### Personal data

Name: **Lone Nikolajsen**  
Date of birth: 28<sup>th</sup> October 1960  
Private address: Søsterhøjvej 2, DK-8270 Højbjerg  
Work address: Bygn. 1A, Aarhus Sygehus, Nørrebrogade 44, DK-Aarhus 8000 C  
Telephone: +4589494317  
E-mail: [nikolajsen@dadlnet.dk](mailto:nikolajsen@dadlnet.dk)

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### Education

1988: Medical doctor  
1998: PhD  
2001: Specialist in anaesthesiology  
2005: Specialist in Pain Medicine (SSRI)

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### Bibliography

Peer-reviewed papers: 30 (9 are reviews)  
Poster presentations internationally: Approx. 14  
Invited lectures: Approx. 20-30  
Book chapters: 10  
Various other publications: 11

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### Supervisor Experience

Diploma projects: 3  
PhD projects: 2  
Other: 3

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### Current research interest

Acute postoperative pain; chronic postoperative pain; phantom pain; spinal cord stimulation

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### Awards

2005: "Pain Doctor of the Year" (Danish Association of Anesthesiology and Intensive Care Medicine)

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### List of publications (last 3 years)

1. Nikolajsen L, Brandsborg B, Lucht U, Jensen TS, Kehlet H. Chronic pain following total hip arthroplasty: A nationwide questionnaire study. *Acta Anaesthesiol Scand* 2006; 50: 495-500.
2. Nikolajsen L, Finnerup NB, Kramp S, Vimtrup A, Keller J, Jensen TS. A randomized study of the effects of gabapentin on postamputation pain. *Anesthesiology*, 2006; 105: 1008-1015.
3. Postoperativ kvalmebehandling. *Debatindlæg. Ugeskriftet for Læger* 2006; 168: 810.
4. Flor H, Nikolajsen L, Jensen TS. Phantom limb pain: a case of maladaptive CNS plasticity? *Nature Review Neuroscience* 2006; 7: 873-81.
5. Toftdahl K, Nikolajsen L, Haraldsted V, Madsen F, Tønnesen EK, Søballe K. Comparison of peri- and intraarticular analgesia with femoral nerve block after total knee arthroplasty: A randomized clinical trial. *Acta Orthop* 2007;78: 172-179.
6. Brandsborg B, Nikolajsen L, Hansen CT, Kehlet H, Jensen TS. Risk factors for chronic pain after hysterectomy: A nationwide questionnaire and database study. *Anesthesiology* 2007;106: 1003-1012.



7. Enggaard TP, Scherer C, Nikolajsen L, Andersen C. Langtidsbehandling med spinal cord-stimulation hos en patient med kronisk regional smertesyndrom type 1 og fantomsmerter efter amputation. *Ugeskrift for Læger* 2007; 170: 460
8. Moller JF, Nikolajsen L, Rodt SA, Ronning H, Carlsson PS. Thoracic paravertebral block for breast cancer surgery: a randomized double-blind study. *Anesthesia and Analgesia* 2007; 105: 1848-51.
9. S Koch, P Ahlburg, N Spangsberg, B Brock, E Tønnesen, L Nikolajsen. Oxycodone versus fentanyl in the treatment of early postoperative pain after laparoscopic cholecystectomy: a randomised double-blind study. *Acta Anaesthesiol Scand* 2008, in press.
10. Nikolajsen L, Kristensen AD, Thillemann TM, Jurik AG, Rasmussen T, Kehlet H, Jensen TS. Pain and somatosensory findings in patients 3 years after total hip arthroplasty. *Eur J of Pain* 2008, in press.
11. Nikolajsen L and Koch S. Postamputation pain. In: Rice A, eds. *Textbook of Clinical Pain management*. Edingburgh: Elsevier Limited 2008, in press
12. Nikolajsen L. Phantom limb pain. In: Stannard C, Kalso E, Ballantyne J, eds. *Evidence-based chronic pain management*. London: Hodder Arnold, 2008, in press

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### Personal data

Name: **Torben Bæk Hansen**  
Date of birth: 7<sup>th</sup> January 1960  
Private address: Lyngbakken 5, DK-7500 Holstebro  
Work address: Ortopædkirurgisk Klinik, Regionshospitalet Holstebro, Lægårdvej 12 DK-7500 Holstebro  
Telephone: +4599125369  
E-mail: [atbh@ringamt.dk](mailto:atbh@ringamt.dk)

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### Education

1985: Graduated from Medical School, University of Aarhus  
1994: PhDthesis, University of Odense  
1996: Certification as a specialist in orthopaedic surgery

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### Scientific positions

1999- Associate Professor, University of Aarhus  
2003- Head of the Orthopaedic Research Unit, Regional Hospital Holstebro

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### Bibliography

Peer-reviewed papers: 65  
Abstracts and proceedings: 74  
Invited lectures: 5  
Book chapters: 3

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### Supervisor Experience

Diploma projects: >10 (9. semester forskningsmetodeopgaver for medicinstuderende)  
PhD projects: 3

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### Current research interest

Arthroplasty in hand surgery, especially the CMC joint of the thumb (clinical results and RSA evaluation, research in implant fixation). Clinical research in hand surgery. Research in optimisation of hip and knee arthroplasty patient care and rehabilitation.

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### List of publications (last 3 years)

1. Hansen TB, Jacobsen F, Larsen K. A pregraduate interprofessional training ward is cost effective in treating patients with primary hip- and knee arthroplasty. J Interprof Care. Submitted.
2. Jacobsen F, Fink AM, Marcussen V, Larsen K, Hansen TB. "When working together, you learn about each others competences". J Interprof Care. Submitted.
3. 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 arthroplasty. BMC. Accepted for publication.
4. Larsen K, Hansen TB, Søballe K. Hip arthroplasty patients benefit after accelerated perioperative care and rehabilitation intervention. Acta Orthop. Accepted for publication.

5. Larsen K, Hansen TB, Thomsen PB, Christiansen T, Søballe K. Cost-efficacy of Accelerated Perioperative Care and Rehabilitation Intervention After Total Hip and Knee Arthroplasty. *J Bone Joint Surg Am*. Accepted for publication.
6. Larsen K, Sørensen OG, Hansen TB, Thomsen PB, Søballe K. Accelerated perioperative care and rehabilitation intervention for hip and knee replacement is effective! *Acta Orthop*. Accepted for publication.

### Personal data

Name: **Malene Laursen**  
Date of birth: 30<sup>th</sup> June of 1963  
Private address: Tordenskjoldsgade 33, 4, DK-8200 Aarhus N  
Work address: Silkeborg Regionshospital, Falkevej 3, DK-8600 Silkeborg  
Telephone: +4520265949  
E-mail: [KOMAL@sc.aaa.dk](mailto:KOMAL@sc.aaa.dk)

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### Education

1992: Cand.med. Aarhus University, Denmark  
2001: Ph.D. Aarhus University, Denmark  
2005: Specialist in Orthopaedic Surgery, Denmark

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### Scientific positions

1996: Research fellow, Orhtopedic Hospital, Aarhus, DK  
1997-1999: Research fellow, Orthopaedic Dept. E, Spine section, Aarhus Kommune Hospital, Aarhus, DK  
2000: Research fellow, Orthopaedic Dept. E, Spine section, Aarhus Kommune Hospital, Aarhus, DK  
2005: Chief Surgeon, Department of Orthopaedics, Silkeborg Regionshospital, Silkeborg, DK  
2008: Member of research council, Silkeborg Regionshospital, Silkeborg, DK

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### Bibliography

Peer-reviewed papers: 17  
Abstracts and proceedings: 58  
Invited lectures: 3

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### Supervisor Experience

Diploma projects: Semiquantitative mRNA measurements of osteoinductive growth factors in human iliac-crest bone  
Diploma projects: Localixation and quantification of growth factors in human bone graft

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### Current research interest:

Clinical research in spine, hip and knee surgery

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### List of publications

1. Laursen M, S. Eiskjær, FB. Christensen, K. Thomsen and C. Bünger. Resultat efter operativ behandling af ustabile thoracolumbale columna frakturer. Ugeskr for læger 1999;161:1910-14.
2. Laursen M, Thomsen K, Eiskjær S, Bünger C Functional Outcome after Partial Reduction and 360 degrees Fusion in grade III-V Spondylolisthesis in Adolescent and Young Patients. J Spinal Disord 1999;12:300-6
3. Laursen M, Høy K, E.S. Hansen and C. E. Bünger. Recombinant bone morphogenetic protein-7 as an intracorporal bone growth stimulator in unstable burst fractures in humans: Preliminary results. Eur Spine J. 1999;8:485-490.

4. Bünger C, Laursen M, Hansen ES., Helmvig P, Høy K, Neumann P, Christensen FB. An Algorithm for the surgical treatment of spinal metastasis. *Current opinion in orthopedics* 1999, 10:101-105
5. Lind M, Laursen M, Overgaard S, Jensen TB, Søballe K, Bünger C. Stimulation af knogleheling med vækstfaktorer indenfor Ortopædkirurgien: Ugeskr for læger. 2000;162:6399-403
6. Haisheng L, Laursen, M, Lind M, Shangtai S and Bünger C. The influence of human intervertebral disc-tissue on the metabolism of osteoblast like cells. *Acta Orthopaedica Scandinavica* 2000; 71:503-507
7. Christensen FB, Laursen M, Gelinick J, Eiskjær S, Thomsen K, Bünger C. Interobserver and intraobserver agreement of radiograph interpretation with and without pedicle screw implants: The need for a detailed classification system in posterolateral spinal fusion. *Spine* 2001;26: 543-4.
8. Christensen FB, Laursen M, Gelineck J, Hansen ES, Bünger C. Posterolateral spinal fusion at non-intended levels due to bone graft migration. *Acta Orthop Scand.* 2001 72:354-8.
9. Andersen MS T, Christensen FB, Laursen M, Hoy K, Hansen ES, Bünger C. Smoking as a predictor of negative outcome in lumbar spinal fusion. *Spine* 2001 26:2623-8.
10. Laursen M: "Predictive Parameters of Autogenous Iliac Crest Bone Graft for Lumbar Spinal Fusion: Quantitative and In vitro Qualitative Aspects". Ph.D Thesis. Faculty of Health Sciences, University of Aarhus. November 2001
11. Christensen FB, Hansen ES, Laursen M, Thomsen K, Bünger C: Long-term functional outcome of pedicle screw instrumentation as a support for posterolateral spinal fusion: Randomized clinical study with a 5-year follow-up. *Spine* 2002 15;27:1269-77.
12. Li H, X Zou, Laursen M, Egund N, Lind M, Bünger C. The influence of intervertebral disc tissue on anterior spinal interbody fusion: an experimental study on pigs. *Eur Spine* 2002 11: 476-481.
13. Laursen M, Christensen FB, Bünger C, Lind M. Optimal handling of fresh cancellous bone graft: different peroperative storing techniques evaluated by in vitro osteoblast-like cell metabolism. *Acta Orthop Scand* 2003 74:490-96
14. Klinisk anvendelse af knoglesubstitutter inden for ortopædkirurgi. Lind M, Jensen TB, Laursen M, Overgaard S, Søballe K, Bünger B. *Ugeskr Laeger.* 2003;165:3712-7. Review
15. Christensen FB, Stender HE, Laursen M, Thomsen K, Bünger C: Supplemental pedicle-screw implementation did not improve long-term functional outcomes after spinal arthrodesis. *J Bone Joint Surg Am.* 2003;85-A:385
16. Laursen M, Christensen FB, Lind M, Hansen ES, Høy K, Gelineck J, Bünger C. In vitro osteoblast-like cell metabolism in spondylodesis- a tool that may predict spinal fusion. *Acta Orthop Scand* 2003 74:730-36
17. Andersen T, Christensen FB, Laursen M, Lund-Olesen L, Gelineck J, Bünger C In vitro osteoblast proliferation as a predictor for spinal fusion mass. *Spine J.* 2003 3:285-8.

### Personal data

Name: **Finn Cilius Nielsen**  
Date of birth: 7<sup>th</sup> of December 1960  
Private address: Vordingborggade 6E, DK-2100 Copenhagen Ø  
Work address: Rigshospitalet, Blegdamsvej 9, DK-2100 Copenhagen Ø  
Telephone: private: +4535436401, work: +4535453016

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### Education

1986: Medical Doctor, University of Copenhagen.  
1993: Doctora thesis: "Insulin-like Growth Factor II: mRNA, Receptors and Biological Actions". University of Copenhagen  
2007: Medical specialist in Clinical Biochemistry.

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### Appointments

1986–1994: Resident, Dept. Clinical Biochemistry, Rigshospitalet and Bispebjerg Hospital, University of Copenhagen.  
1995: Consultant, Dept. Clinical Biochemistry, Rigshospitalet, University of Copenhagen.  
1999–2004: Research professor, Hallas Møller, Stipend, Novo Nordisk.  
2004: Professor of Clinical Molecular Biology, Dept. Clinical Biochemistry, Rigshospitalet, University of Copenhagen.

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### Bibliography

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| Original articles:                       | 97 |
| Reviews, textbooks and textbook chapters | 22 |
| Letters and comments                     | 17 |

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### Other academic activities

1995: Corresponding Editor – Scandinavian Journal of Clinical and Laboratory Investigation.  
2002: Committee member of "Selskab for Teoretisk og Anvendt Medicin"  
2003: Committee member of "Biologisk Selskab".  
2005: Chairman of The Danish Medical Research Council.  
Prizes:  
1991: Awarded Architect Holger Hjortenbergs and Dagmar Hjortenbergs Foundation Prize.  
1994: Awarded Consul-general Valdemar Joseph Glückstadts Diabetes Prize.  
1994: Winner of the Astrup Prize in Clinical Biochemistry.  
1996: Awarded Misse and Valdemar Rissom Cancer Prize.  
1997: Awarded Consultant Johan Boserup and Lise Boserup Prize.  
1997: Awarded Fabrikant Ulrik Brinch and wife Marie Brinch Prize.  
1999: Danish cancer society. Junior Scientist's Prize.  
1999: Medal of Honour, Danish Society of Theoretic and Applied Therapy.  
2001: Awarded Christensson-Ceson's Family Foundation Prize.  
2002: Awarded the Odd Fellow Prize.  
2003: Awarded C.C. Klestrup and wife Henriette Klestrup's Prize.  
2003: Awarded Lise and Gunnar Wærum's Prize.

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**Appendix 3: Proposal for 5-year budget**

|                          |                      |  | Year          |              |              |              |              |               |
|--------------------------|----------------------|--|---------------|--------------|--------------|--------------|--------------|---------------|
|                          |                      |  | 2008          | 2009         | 2010         | 2011         | 2012         | 2013          |
| Salaries                 |                      |  |               |              |              |              |              |               |
| VIP*                     | Eastern <sup>1</sup> |  | 0.75<br>(1,5) | 1.5<br>(3)   | 1.5<br>(3)   | 1.5<br>(3)   | 1.5<br>(3)   | 0.75<br>(1,5) |
|                          | Western <sup>2</sup> |  | 0.75<br>(1,5) | 2.0<br>(4)   | 1.5<br>(3)   | 1.5<br>(3)   | 1.5<br>(3)   | 0.6<br>(1,2)  |
| TECH+                    | Eastern <sup>1</sup> |  | 0.6<br>(1,5)  | 1.2<br>(3)   | 1.2<br>(3)   | 1.2<br>(3)   | 1.2<br>(3)   | 0.6<br>(1,5)  |
|                          | Western <sup>2</sup> |  | 0.6<br>(1,5)  | 1.4<br>(3,5) | 1.4<br>(3,5) | 1.4<br>(3,5) | 1.4<br>(3,5) | 0.7<br>(1,75) |
| Apparatus                |                      |  | 2.0           |              |              |              |              |               |
| Project related expenses |                      |  | 0.1           | 0.1          | 0.1          | 0.1          | 0.1          | 0.1           |
| Project coordination     |                      |  | 0.6           | 0.6          | 0.6          | 0.6          | 0.6          | 0.2           |
| Other                    |                      |  | 0.1           | 0.1          | 0.1          | 0.1          | 0.1          | 0.1           |
| <b>Total per year</b>    |                      |  | 5.5           | 6.9          | 6.4          | 6.4          | 6.4          | 3.05          |
| <b>Total cum.</b>        |                      |  |               | 12.4         | 18.8         | 25.2         | 31.6         | 34.65         |

Amount in millions of DKK. Man-years in parentheses.

<sup>1</sup> Eastern Danish Partner – Department of Orthopaedic Surgery, Hvidovre Hospital and Section for Surgical Pathophysiology, Rigshospitalet, Copenhagen University Hospital

<sup>2</sup> Western Danish Partner – Department of Orthopaedic Surgery, Aarhus University Hospital, Regional Hospital Silkeborg and Regional Hospital Holstebro

\*VIP salary per year 500,000 DKK, man-years in parentheses

+TECH salary (including two secretaries) per year 400,000 DKK, man-years in parentheses

**Commentaries:**

We are applying for **34.65** million DKK. The budget is intended to cover personnel and new apparatus as project-related expenses at the clinical departments.

We have allocated six VIPs and six technicians to the project.

The apparatus includes: Navigation system for orthopaedic surgery.

Project coordination covers: booking, coordination between collaborating departments, patient related phone and letter correspondence, filing and documentation according to GCP guidelines.

**Appendix 4: Reduced budget**

|                          |                      |  | Year          |               |               |               |               |
|--------------------------|----------------------|--|---------------|---------------|---------------|---------------|---------------|
|                          |                      |  | 2009          | 2010          | 2011          | 2012          | 2013          |
| Salaries                 |                      |  |               |               |               |               |               |
| VIP*                     | Eastern <sup>1</sup> |  | 0.75<br>(1,5) | 0.75<br>(1,5) | 0.75<br>(1,5) | 0.75<br>(1,5) | 0.75<br>(1,5) |
|                          | Western <sup>2</sup> |  | 0.75<br>(1,5) | 0.75<br>(1,5) | 0.75<br>(1,5) | 0.75<br>(1,5) | 0.75<br>(1,5) |
| TECH+                    | Eastern <sup>1</sup> |  | 1.0<br>(2,5)  | 1.0<br>(2,5)  | 1.0<br>(2,5)  | 1.0<br>(2,5)  | 1.0<br>(2,5)  |
|                          | Western <sup>2</sup> |  | 1.0<br>(2,5)  | 1.0<br>(2,5)  | 1.0<br>(2,5)  | 1.0<br>(2,5)  | 1.0<br>(2,5)  |
| RSA                      |                      |  | 0.2           | 0.2           | 0.2           | 0.2           | 0.2           |
| Lab analysis             |                      |  | 0.1           | 0.1           | 0.1           | 0.1           | 0.1           |
| Ultrasound               |                      |  | 0.1           | 0.1           | 0.1           | 0.1           | 0.1           |
| Project related expenses |                      |  | 1.0           | 1.0           | 0.5           | 0.5           | 0.5           |
| Project coordination     |                      |  | 1.0           | 1.0           | 0.5           | 0.5           | 0.5           |
| Other                    |                      |  | 0.1           | 0.1           | 0.1           | 0.1           | 0.1           |
| <b>Total per year</b>    |                      |  | 6.0           | 6.0           | 5.0           | 5.0           | 5.0           |
| <b>Total cum.</b>        |                      |  |               | 12.0          | 17.0          | 22.0          | 27.0          |

Amount in millions of DKK. Man-years in parentheses.

<sup>1</sup> Eastern Danish Partner – Department of Orthopaedic Surgery, Hvidovre Hospital and Section for Surgical Pathophysiology, Rigshospitalet, Copenhagen University Hospital

<sup>2</sup> Western Danish Partner – Department of Orthopaedic Surgery, Aarhus University Hospital, Regional Hospital Silkeborg and Regional Hospital Holstebro

\*VIP salary per year 500,000 DKK, man-years in parentheses

+Tech. salary (including two secretaries) per year 400,000 DKK, man-years in parentheses

**Commentaries:**

We apply for **27.0** million DKK. The budget is intended to cover personnel and project related expenses at the clinical departments.

We have allocated four VIPs and six technicians to the project.

Project coordination cover: booking, coordination between collaborating departments, patient related phone and letter correspondence, filing and documentation according to GCP guidelines.



## **Appendix 5: Description of institutional collaboration**

The Centre for Fast-track Hip and Knee Surgery, formed by the joint competencies and existing cooperation of the Department of Orthopaedics Aarhus University Hospital, Department of Orthopaedic Surgery, Hvidovre Hospital, Copenhagen University Hospital, and Section for Surgical Pathophysiology, Rigshospitalet, Copenhagen University Hospital has the broad base of clinical knowledge and multidisciplinary expertise to develop high quality projects in a wide range of clinically relevant target areas. The two principal investigators have documented qualifications for clinical research at a high international level, based on a large international framework and collaboration.

At the University of Aarhus, the clinical orthopaedic surgical research tradition was established by Professor Otto Sneppen in 1980. Today, the research group is managed by Professor Kjeld Søballe, MD. The group currently consists of 13 post.docs, 29 Ph.D. students and approx. 15 pregraduate research students. The group has a wide national cooperation with surgical as well as medical departments and a strong international cooperation with, among others, the USA, New Zealand, Finland, Holland and Ireland. The group has a solid background in clinical as well as basic research and rewarding interdisciplinary cooperation that transverses traditional professional groups. The core research areas include aetiology, prophylaxis and treatment of illnesses in joints and muscles. The research activity in the group is steadily increasing. The total number of published articles is now 182.

At the University of Copenhagen, Henrik Kehlet has performed surgical outcome research within all aspects of perioperative pathophysiology, organisational studies, and more, and synthesized this into the concept of "fast-track surgery". A concept that has fostered over 700 publications, over 12 doctoral theses and several PhD.-studies. A large research group in several Copenhagen university hospitals has been established between different surgical specialities, departments of anaesthesiology and nursing care, and adjusted to high-impact international implications, by widespread international collaboration.