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# DEX-2-TKA - DEXamethasone twice for pain treatment after Total Knee Arthroplasty. A protocol for a randomized, blinded, three-group multicentre clinical trial

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## Title page:

DEX-2-TKA - DEXamethasone twice for pain treatment after Total Knee Arthroplasty. A protocol for a randomized, blinded, three-group multicentre clinical trial

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## Abstract

**Background:** Multimodal analgesia is considered the leading principle for postoperative pain treatment, but no gold standard after total knee arthroplasty (TKA) exists.

**Aim:** To investigate the beneficial and harmful effects of one or two doses of 24 mg intravenous dexamethasone as part of a multimodal analgesic regimen (paracetamol, NSAID and perioperative local infiltration analgesia) after TKA. We hypothesise that addition of dexamethasone will reduce postoperative opioid consumption.

**Methods**: 'DEXamethasone twice for pain treatment after TKA' (DEX-2-TKA) is a randomized, blinded, three-group multicentre clinical trial. Participants will be randomized to one of three groups: placebo,

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single dose of dexamethasone, or two consecutive doses of dexamethasone. Participants, treatment providers, and investigators will be blinded to the allocated intervention. The primary outcome is total opioid consumption (units of morphine equivalents) 0-48 h postoperatively. Inclusion criteria: unilateral, primary TKA; age ≥18 years; American Society of Anesthesiologists (ASA)-Score 1-3; Body Mass Index ≥18 and ≤40; for women – not pregnant; and written informed consent. Exclusion criteria: allergy or contraindications against trial medication; daily use of high dose opioid and/or use of methadone/transdermal opioids; daily use of systemic glucocorticoids; dysregulated diabetes; and patients suffering from alcohol and/or drug abuse. Four-hundred-and-eighty-six eligible participants are needed to detect or discard a difference of 10 mg morphine equivalents 0-48 h postoperatively maintaining a family-wise error rate of 0.05 and a power of 90% for the three possible pairwise comparisons.

**Discussion:** Recruiting is planned to commence September 2018 and expected to finish March 2020.

**Trial registration:** EudraCT: 2018-001099-39 (08/06-18); ClinicalTrials.gov: NCT03506789 (24/04-2019)

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## Background

Effective postoperative pain management is crucial for the recovery of patients undergoing surgery.[1] It facilitates early mobilisation, nutrition, and resumption of daily activities.[1] Multimodal analgesia is generally considered the leading principle for postoperative pain treatment.[2]

Total knee arthroplasty (TKA) is a frequent procedure. In 2015, approximately 700.000 TKAs were performed in the US alone.[3] TKA is associated with severe postoperative pain[4] which is a major concern among patients.[5] Patients undergoing TKA are often elderly with concomitant comorbidities, and a significant number develop persistent postoperative pain[6,7] which may lead to chronic opioid consumption .[8] Consequently, alleviation of TKA-related pain is of utmost importance, but is a clinical challenge and often includes significant amounts of opioids with adverse effects.[4,9] A multitude of different analgesics and analgesic methods have been investigated for TKA pain treatment, but currently the literature does not present a gold standard.[9]

Glucocorticoids (GCCs) have been used for treatment of inflammatory diseases for more than 60 years[10] and have several potential beneficial effects, as well as potential adverse effects, the latter especially when administered in higher doses and for longer term.[11] However, in contrast to previous concerns, based on the available literature, perioperative administration of GCC does not seem to increase the incidence of infection or symptomatic hyperglycaemia.[12] In a meta-analysis of 56 trials with 5607 patients undergoing non-cardiac surgery and receiving a wide dose range of GCC but with a varying follow-up period (7-30 days or not reported), the incidences of any infection, deep wound infection, symptomatic hyperglycaemia or other serious adverse events (SAE) were similar compared with the placebo group.[13]

Recent trials, including a variety of surgical procedures, indicated postoperative opioid sparing and analgesic effects of dexamethasone (DXM), which is a GCC frequently used for anti-emetic treatment.[13–15] In a systematic review including 24 randomized clinical trials (RCTs) and 2751 patients, DXM at doses up to 0.2 mg/kg, resulted in smaller but significant reductions of both postoperative opioid usage and pain scores for the first 24-hours, but with no further advantage of doses >0.2 mg/kg.[15] Only a limited number of trials with higher doses of GCC was, however, included in that review. Moreover, a single high preoperative dose of methylprednisolone 125 mg (equivalent to 25 mg DXM) compared with placebo[11] demonstrated significantly reduced opioid requirements, pain levels, C-reactive protein (CRP) levels, postoperative nausea and vomiting (PONV), and fatigue.[16] This trial, however, only included 48 patients

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and needs confirmation. Thus, it is presently unknown if patients will benefit from a higher perioperative dose of GCC. **Table 1** offers an overview of the most recent systematic reviews on the subject.

Thus, the present study is motivated by that, GCCs have indicated some analgesic effects in the surgical setting but the effects are unclear based on current evidence. Furthermore, it is unknown if higher, or repeated doses, will demonstrate an improved effect. Finally, long-term effects are insufficiently assessed.

**Aim**

The purpose of this RCT is to investigate the beneficial and harmful effects of one or two doses of 24 mg intravenous (i.v.) dexamethasone as part of a multimodal analgesic regimen after TKA.

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## Methods/design

'DEXamethasone twice for pain treatment after TKA' (DEX-2-TKA) is a randomized, blinded, three-group multicentre clinical trial (**figure 1**)(**figure 2)**. Participants will be randomized to one of three groups receiving either: placebo, a single dose of DXM, or two consecutive doses of DXM. All three groups will additionally receive a standard regimen of paracetamol, NSAID (ibuprofen), and local infiltration analgesia (LIA).

### Hypothesis

Our primary hypotheses are that the addition of DXM to the standard regimen will reduce postoperative opioid consumption, and that two doses of DXM will further reduce postoperative opioid consumption.

### Inclusion criteria

Patients meeting all the following criteria are eligible for inclusion in the trial:

- scheduled for unilateral, primary TKA
- age ≥18 years
- American Society of Anesthesiologists (ASA)-Score 1-3
- body Mass Index ≥18 and ≤40
- for women in the fertile age, negative urine human chorionic gonadotropin (hCG) test (pregnancy test) and use of anti-conception
- written informed consent

### Exclusion criteria

Patients meeting one or more of the following criteria are not eligible for inclusion in this trial:

- patients who cannot cooperate with the trial
- concomitant participation in another trial involving medication
- patients who cannot understand or speak Danish
- patients with allergy to medication used in the trial
- patients with daily use of high dose opioid (>oral morphine or oxycodone 30 mg/day or tramadol 150 mg/day) or any use of other opioids including methadone and transdermal opioids
- patients with daily use of systemic GCC (within three months before the surgery)

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- contraindications against ibuprofen or paracetamol, including previous gastric ulcer, known heart failure, liver failure, renal failure (eGRF <60 ml/kg/1.73m$^2$), or thrombocytopenia (<100 × 10$^9$l/l); or against GCC treatment.
- dysregulated diabetes (investigator's judgement)
- patients suffering from alcohol and/or drug abuse (investigator's judgement)

**Randomization**

Participants will be randomized in a 1:1:1 ratio. The randomization will be performed by Skanderborg Pharmacy (Region of Central Denmark) using randomization.com with varying (unknown) blocks of 3*6, 2*9 or 1*18. Allocation numbers in varying blocks of 18 in total, will be distributed to the sites via the clinical trial management database software EasyTrial.net. Each participant entering the trial will be given a unique allocation number identifying the trial drug.

**Outcome measures**

*Primary outcome*

Total opioid consumption measured in units of morphine equivalents 0-48 h postoperatively. Opioids will be administered as 1) patient controlled analgesia (PCA) morphine (0-24 h), 2) on demand oral morphine (24-48 h), and 3) any additional escape opioid (converted to i.v. morphine equivalents) (0-48 h).

*Secondary outcomes*

- visual analogue scale (VAS)-pain scores
    - during active 45 degrees flexion of the knee at 24 and 48 h postoperatively
    - at rest at 24 and 48 h postoperatively
    - highest score during 0-24 h and 24-48 h
- proportion of participants with one or more adverse event in the period 0-48 h postoperatively

*Exploratory outcomes*

- proportion of participants with one or more severe adverse event (SAE), including death, within 90 days after surgery (SAE defined according to ICH-GCP-guidelines, except 'prolongation of hospitalisation').
- total i.v. morphine consumption 0-24 h
- total oral morphine consumption 24-48 h
- VAS-pain scores
    - with active 45 degrees flexion of the knee at 6 h postoperatively

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    - at rest at 6 h postoperatively
    - average score during 0-24 h and 24-48 h
- timed up and go (TUG) test at 24 and 48 h including maximum pain during the TUG test
- opioid related adverse events (AE)
    - level of nausea, sedation and dizziness at 6, 24 and 48 h
    - number of vomiting episodes 0-24 and 24-48 h
    - consumption of anti-emetics 0-24 h and 24-48 h
- quality of sleep assessed at 24 h and at 48 h
- level of fatigue at 24 h and 48 h
- questionnaire on pain, sleep and overall satisfaction for postoperative day (POD) 3-7
- proportion of participants with permanent use of opioids 90 days after surgery
- 90 days follow-up with EQ-5D-5L
- 90-days follow-up with Oxford-Knee-Score

Methods of measurements are as seen in the **Appendix 1**

**Trial interventions**

Trial period: from randomization to 90 days postoperatively.

Intervention period: from the participant receives the first intervention to 48 h postoperatively.

Treatments (three groups A-C)

- *Intervention A:* dexamethasone 24 mg i.v. given after induction of anaesthesia and repeated at 24 h postoperatively (±1 h)
- *Intervention B:* dexamethasone 24 mg i.v. given after induction of anaesthesia and placebo (isotonic saline) i.v. at 24 h postoperatively (±1 h)
- *Intervention C:* placebo (isotonic saline) i.v. given after induction of anaesthesia and repeated at 24 h postoperatively (±1 h)

*Concomitant medication*

Standard premedication: paracetamol (PCM) 1 g + ibuprofen (IBU) 400 mg orally 1 hour before surgery

Standard anaesthesia: spinal anaesthesia is preferred

- For spinal anaesthesia, bupivacaine 0.5% HEAVY 10 – 15 mg without opioids is used. If sedation is needed, propofol infusion is preferred.

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- For general anaesthesia, propofol- and remifentanil infusions are preferred. Alternatively, sevoflurane-based anaesthesia is allowed. Fifteen minutes before end of surgery sufentanil i.v. 0.3 micrograms/kg is given.

All participants, regardless of method of anaesthesia, will receive ondansetron 4 mg intraoperatively as PONV prophylaxis.

Standard postoperative pain and nausea management

- PCM 1 g + IBU 400 mg orally four times daily
- Local infiltration analgesia (LIA) intraoperatively 150 ml ropivacaine injected by surgeon into rear and front capsule and intraarticular. No NSAIDs added in the mixture.
- PCA-morphine (0-24 h), bolus 2 mg, lockout time 10 min. Mixture: morphine 1 mg/ml
- Morphine 10 mg tablet (24-48 h) on-demand
- If there is need for morphine in addition to the PCA pump in the first 1 h after the anaesthesia has ceased, at the postanaestesia care unit (PACU), additional bolus doses of 2 mg morphine i.v. may be given on participants' request
- If participants experience moderate to severe nausea, ondansetron 1 mg may be given up to a maximum of 16 mg/day. If symptoms persist, droperidol (DHB) 0.625 mg i.v. may be used to a max of 1.25 mg/day

*Other medications*

Treatment of pain after the intervention period will follow local departments' guidelines. Analgesic medications other than those stated above are not permitted from the participant receives the first intervention to 48 h postoperatively. This includes other opioids, chlorzoxazone, antidepressants, steroids, and gabapentinoids. Morphine, oxycodone, or tramadol in non-excluding doses as well as gabapentinoids and antidepressants are only permitted if the participant continues an already instituted treatment from before surgery. All non-analgesic medications are permitted at the discretion of the attending physician.

**Blinding**

Trial medication is masked by Skanderborg Pharmacy (Region of Central Denmark) and is packed and labelled by the pharmacy in accordance with the good manufacturing practice (GMP). DMX and placebo will be matching and will be indistinguishable. Participants, administrators of the intervention, treatment providers, outcome assessors, investigators, and conclusion drawers will be blinded to both the

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intervention and the allocation sequence. Statistical analyses will be performed with the three intervention groups coded as '1', '2' and '3' by two independent blinded statisticians. Three blinded conclusions will be drawn by the Steering Committee assuming that either '1', '2' or '3' is the placebo group. Based on these three blinded conclusions, three abstracts will be written and published along with the main publication.

Skanderborg Pharmacy retains the non-blinded block randomized allocation sequence list, which will remain unrevealed until the data has been analysed and abstracts[17] and conclusions covering the different interpretations of the trial results have been agreed upon by the Steering Committee.

**Safety**

AE, adverse reactions (AR), SAEs, serious adverse reactions (SARs) and suspected unexpected serious adverse reactions (SUSARs) will be recorded in the intervention period and reported to the relevant authorities according to guidelines from ICH-GCP and the Danish Medicines Agency.

**Withdrawal of participants**

*Discontinuation of individual participants*

If a SAE occurs in the intervention period, the investigator will consult the principal investigator/sponsor, to determine whether it is feasible for the participant to continue. If the participant is withdrawn, we will ask whether we may record data.

Blinding of the intervention can be broken if the treatment of the participant requires knowledge of the randomization code. This can be done by the investigator without restrictions. Breaking of the code can be done by accessing the sealed opaque envelope of the investigator and the date and reason must be recorded. The investigator will ensure the necessary procedures and expertise to handle any emergency situation that may arise during the trial.

*Participant withdrawal*

A participant who has not completed the trial is a participant who has received the first intervention and does not allow for continued data recording. If a participant does not complete the trial, an account will be given as to whether and how this participant and data is followed in the trial.

**Statistics**

*Sample size estimation and power calculation*

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To maintain an overall familywise error rate of 0.05, the sample size estimation is based on pairwise comparisons of the primary outcome between three groups (three comparisons: 'A' vs. 'B', 'A' vs. 'C' and 'B' vs. 'C') which results in a Bonferroni adjusted risk of type I error of 0.0167. To detect or discard a minimal important difference of 10 mg morphine i.v. consumed in 48 hours with a power of 90%, and with an estimated standard deviation of 22.7 mg over 48 hours (unpublished data from 46 patients at Næstved Hospital), we need to randomize a total of 423 participants (141 in each group). We have chosen 10 mg morphine as our minimal clinically important difference (MCID), which corresponds to a change of 22% and is within an often cited MCID range (20-30%) for opioid reduction.[18,19] Sample size is calculated with PS Power and Sample Size Calculations (Version 3.0, January 2009, © William D. Dupont and Walton D. Plummer). As we do not expect data for our primary outcome to be normally distributed,[20] we will add a surplus of 15%, thus 162 participants will be included in each group, for a total of 486 eligible participants.

*Statistical methods*

The trial will be completed when 486 participants are included in the intention-to-treat population.

The primary analysis of the primary outcome, morphine consumption within 48 h, will be a pairwise comparison of the consumption of morphine between the three groups stratified for site by van Elteren test.[21] 98.34% confidence intervals for the difference in medians will be provided by boot-strapping.

Secondary analyses include per protocols analyses of all outcomes. The per protocol population will exclude participants with major protocol violations. The definitions of the intention-to-treat population, the per protocol population, and major protocol violations are presented in **Appendix 2**.

A detailed statistical analysis plan will be published prior to enrolment of the last participant.

**Data collection**

An electronic case report form (CRF) will be completed for each participant included in the trial. Only the investigators or their assistants will enter data in the CRF. The CRF is hosted and maintained by EasyTrial Aps (Aalborg, Denmark).

Data will be collected directly from the participants by trial investigators or educated clinical personnel and from the electronic participant's chart, the civil registration system through Statistics Denmark, the Danish National Patient Registry and the Danish National Pharmaceutical Statistic Registry. All data will be handled according to the General Data Protection Regulation. Data will be stored in five years after finishing the trial. Afterwards all paper material will be destroyed, and electronic data will be completely anonymised.

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**Monitoring**

The trial will be externally monitored by The University of Copenhagen's and The University of Southern Denmark's Good Clinical Practice (GCP) units according to the latest legislation.

**Ethical consideration**

The trial will be conducted in accordance with the principles of the Declaration of Helsinki in compliance with the protocol, approved by the competent authority and ethics committee, and according to GCP standards.[22] No deviation from the protocol will be implemented without the prior review and approval of the regulatory authorities except where it may be necessary to eliminate an immediate hazard to the trial participants.

**Data analysis and publication**

Before revealing the randomization list, two dedicated trial statisticians will independently perform the data analyses according to the statistical analysis plan, and the Steering Committee will agree upon written abstracts covering all possible combinations. The final manuscript will contain the correct pre-made abstracts. The protocol follow the standard protocol items: recommendations for interventional trials and the manuscript will follow consolidated standards of reporting of randomized trials (CONSORT) Statement.[23] Authorship will be granted following the guidelines from the International Committee of Medical Journal Editors.[24] Funding sources will have no influences on the interpretation of data. The full, anonymized dataset will be published no longer than 18 months after completion of the trial. The trial is registered at clinicaltrials.gov with identifier: NCT03506789.

*Substudies*

- One-year follow-up with EQ5D5L + Oxford-Knee-Score and need for medical attention and/or intervention
- Analyses of high and low pain responders
- At selected sites, troponin levels at 24 and 48 h, and cardiovascular events
- At selected sites, establishment of a bio bank (blood samples) for further research of perioperative immune function and the related effect of DXM

**Timeline**

2018: Application for approval from the Danish Medicines Agency, the Ethics Committee and the Danish Data Registration Agency. Development of an eCRF and randomization website

2018–2020: Enrolment of participants

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2020: Data analyses, writing and submission of the manuscript

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## Discussion

With the present trial, we expect to be able to determine if one or two high doses of DXM has a postoperative analgesic effect in TKA, as part of a multimodal analgesic regimen including paracetamol, ibuprofen and LIA.

Our trial has several strengths. Besides being a randomized, blinded and placebo-controlled trial with low risk of bias, we expect high external validity, as the trial is both multicentre and pragmatic (i.e. the broad in- and exclusion criteria) mimicking clinical reality as much as possible. Hence, we expect the findings from this trial to be generally applicable for TKA. Furthermore, the trial has rigorous follow-up with questionnaires on day 3 to 7, an interview on day 90 and data from the comprehensive Danish public health registries.

**Limitations**

We chose a MCID of 10 mg morphine consumption the first 48 hours postoperatively. This is, arguably, a relatively low difference for 48-hour use. However, the analgesic effect of DXM is investigated as part of a multimodal analgesic regimen as the fourth non-opioid analgesic. Firm evidence for analgesic effect of combining more than two non-opioid analgesics is virtually none existent,[25,26] and we expect that more analgesics in combination would lead to less effect of each added analgesic.[27] We therefore chose a relatively low MCID in order not to miss any opioid-reducing effect of DXM. Another limitation of the trial is, that the expected power to detect differences in AE and SAE between the three groups is relatively low, although detected SAE in the recent PANSAID[18] trial found an overall incidence of SAE to be 14% within 90-days of total hip arthroplasty.

It is possible that the effect of DXM may demonstrate a protracted effect lasting after the 48 h intervention period, making the difference between one and two doses of DXM difficult to distinguish until after 48 h. We have tried to count for this by a supplemental patient diary on pain for postoperative day 3-7.

We expect the results from this trial to be of high quality and with low risk of bias regarding the role of one or two doses of dexamethasone in a multimodal analgesic regimen and be able to conclude whether or not DXM is recommended for patients undergoing TKA.

**Trial status**

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Currently, more than 290 participants have been enrolled in the trial. We expect the enrolment period to end in March 2020 at the latest. The trial status can be seen at the trial website http://appraz.dk/projects/dex-2-tka/index.html.

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Table 1, Overview of the most recent systematic reviews of glucocorticoids for paint treatment in non-cardiac surgery:

| Ref | Drug and administration | n (active/placebo) | Surgical population | Pain compared with placebo | Opiod consumption in control groups | Opiod consumption compared with placebo (95% CI) | Opiod related adverse effects | Comment |
|---|---|---|---|---|---|---|---|---|
| De Oliveira et al.[15] | Single-dose perioperative intravenous dexamethasone in adult patients. Comparisons were stratified by dose into three groups: low-dose (≤ 0.10 mg/kg), intermediate-dose (0.11–0.20 mg/kg), and high-dose (≥ 0.21 mg/kg) dexamethasone. | 2751 (24 trials) | Mixed minor-major surgery (not dental) | Overall significant reduction at rest and during movement, both at 4 h and 24 h post-operatively | No data | Opioid consumption was reduced to a similar extent with moderate-dose: SMD = −0.82 (−1.30; −0.42) and high-dose: −0.85 (−1.24; −0.46) dexamethasone, but not reduced with low-dose dexamethasone: −0.18 (−0.39; | Not reported | Glucocorticoids most often assessed in multimodal analgesia trials. |

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| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | | | | 0.03) (number of mg not provided) | | |
| Waldron et al.[28] | Single-dose perioperative intravenous dexamethasone 1.25–20 mg in adult patients. | 2997/2799 (45 trials) | Mixed minor-major surgery (not dental) | Overall significant reduction, both at 2 h and 24 h post-operatively | No data | Fourteen studies (2157 patients) recorded opioid use at 24 h after operation. Patients receiving dexamethasone used significantly less morphine equivalents in the first 24 h after surgery (MD = −2.33 (−0.26; −4.39) mg, *P* = 0.03). This represents a 10.3% reduction in opioid consumption compared | Not reported | Glucocorticoids most often assessed in multimodal analgesia trials. |

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| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | | | | with controls | | |
| Shen et al.[29] | Single-dose perioperative intravenous or intraarticular methylprednisolone 40-125 mg in adult patients. | 128/121 (4 trials) | Total knee arthroplasty | Overall significant reduction, both at 6 h, 12 h and 24 h post-operatively | No data | Four studies (248 patients) recorded opioid use at 24 h after operation. (WMD = −3.651, 95% CI: −5.909 to −1.393, P = 0.002) | Overall significant reduced risk of nausea and vomiting | Glucocorticoids most often assessed in multimodal analgesia trials. |
| Zhou et. al[30] | Single-dose or two doses perioperative intravenous or periarticular dexamethasone 5-10 mg in adult patients. | 291/285 (6 trials) | Total knee arthroplasty | Overall significant reduction, both at 12 h and 48 h post-operatively | No data | Six studies (576 patients) recorded opioid use at 24 h after operation. (WMD = -2.192, 95% CI: -4.484 to 0.099, P = .061) | Overall significant reduced risk of nausea and vomiting | Glucocorticoids most often assessed in multimodal analgesia trials. |
| Fan et al[31] | Single-dose or two doses perioperative intravenous dexamethasone 10-40 mg in adult patients. | 110/107 (3 trials) | Total Hip arthroplasty | Overall significant reduction, both at 24 h and 48 h | No data | Three studies (217 patients) recorded opioid use at 24 h after operation. (SMD = -0.63, 95% | Overall significant reduced risk of nausea | Glucocorticoids most often assessed in multimodal analgesia trials. |

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| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | | post-operatively | | CI: -0.91 to -0. 35, P < .001) | | |
| Yang et. al[32] | Single-dose or two doses perioperative intravenous dexamethasone 5-40 mg, hydrocortisone 200 mg or methylprednisolone 125 mg in adult patients. | 157 (5 trials) | Total Hip arthroplasty | Overall significant reduction, both at 6 h, 24 h and 48 h but not at 72 h post-operatively | No data | Five studies (157 patients) recorded total opioid use postoperative (WMD = -9.36, 95% CI -12.33 to -6.38, P = .000) | Overall significant reduced risk of postoperative nausea and vomiting | Glucocorticoids most often assessed in multimodal analgesia trials. |
| Li et. al[33] | Single-dose perioperative intravenous dexamethasone 8-40 mg, hydrocortisone 200 mg or methylprednisolone 125 mg in adult patients. | 199 (4 trials) | Total Hip arthroplasty | Overall non-significant reduction, both at 24 h and 48 h post-operatively | No data | Four studies (199 patients) recorded total opioid use postoperative (WMD = -15.68, 95% CI -24.60 to -6.75, P = .001) | Overall significant reduced risk of postoperative nausea and vomiting | Glucocorticoids most often assessed in multimodal analgesia trials. |

CI: Confidence Interval; MD; Mean Difference; SMD: Standardized Mean Difference; WMD: Weighted Mean Difference

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Figure 1, DEX-2-TKA Flowchart

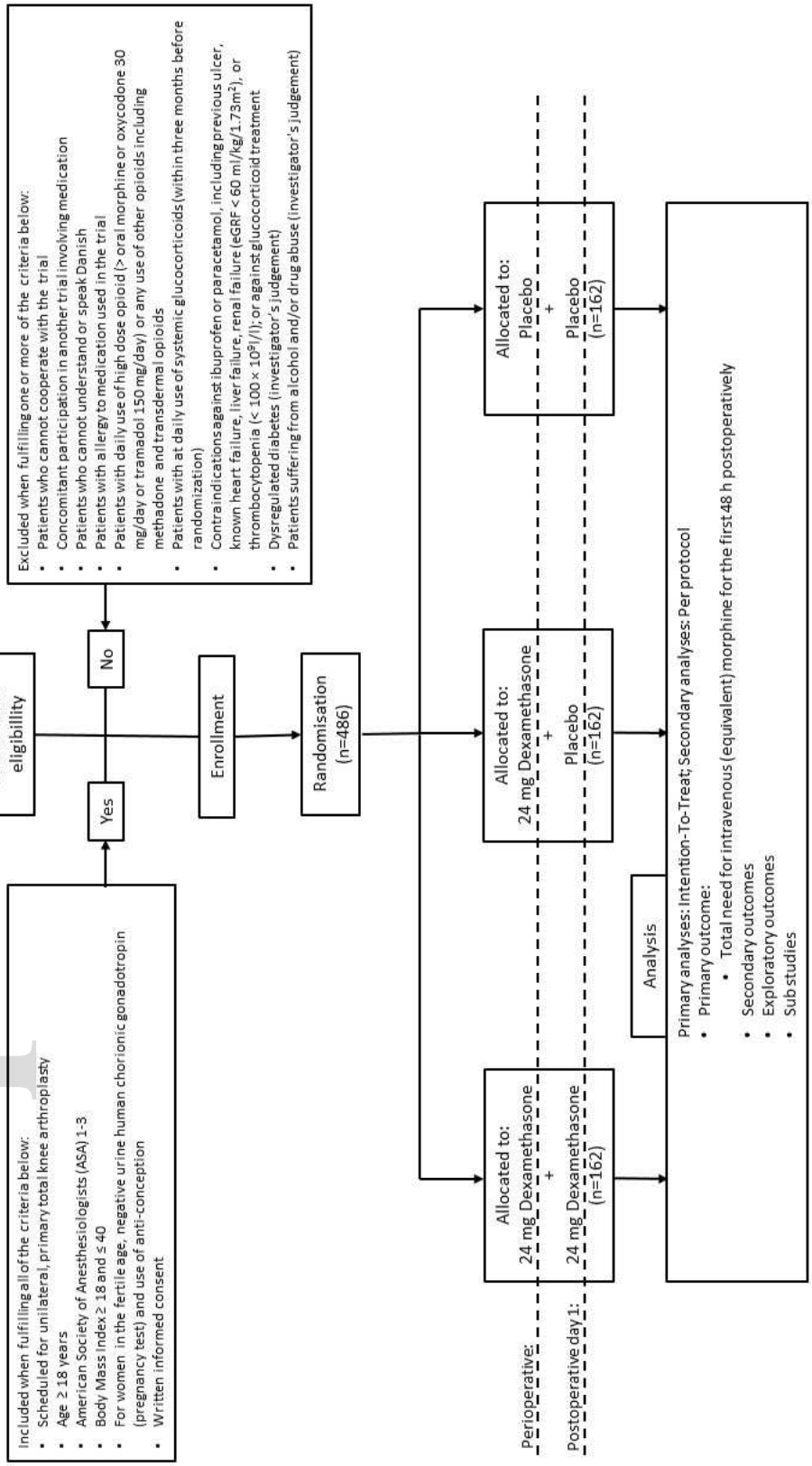


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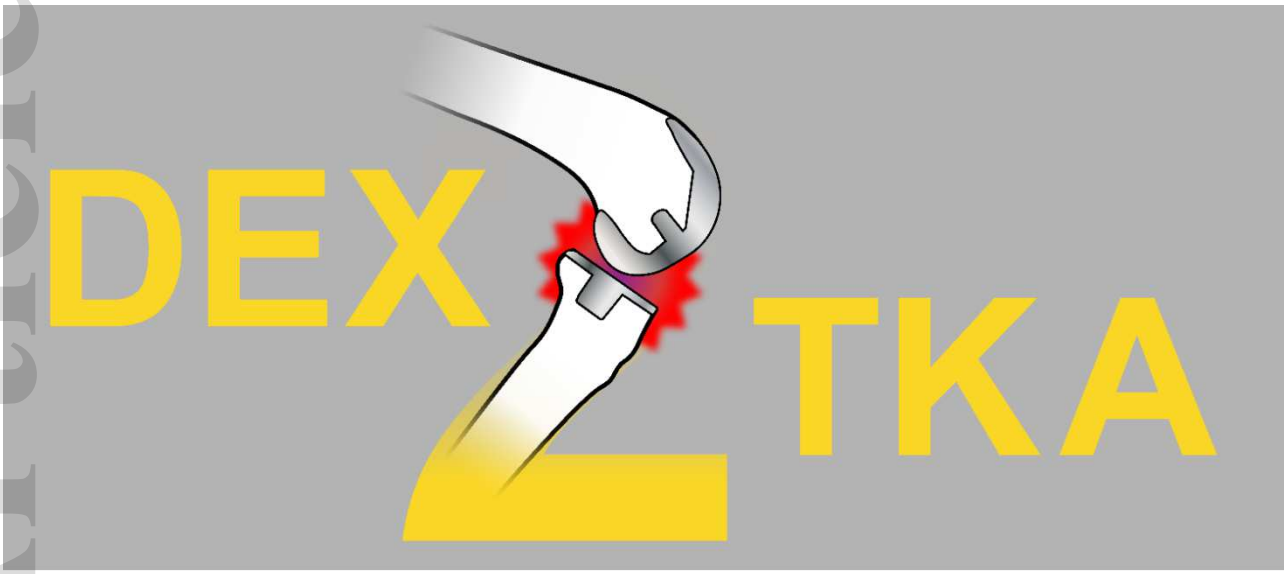
Figure 2, DEX-2-TKA Logo

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Appendix 1, **Methods of measurements**

The total amount of morphine (mg) delivered in the period 0-48 h will be recorded. This includes PCA-morphine (i.v.), oral on demand morphine, morphine administered at the PACU and any other opioid administrated. Oral opioids will be converted to i.v.-eqv. according to table 1 (from supporting information "S2 Appendix" in Karlsen et. al).[9]

The following data, except medicine usage, will be collected by asking the participants:
Participants' pain is registered on a VAS of 100 mm or a numeric ranking scale (NRS) of 0-10: 0 = no pain; 100 or 10 = worst possible pain. NRS is used if the participant answers are obtained by telephone or questionnaire.

Pain at rest, and during 45 degrees active flexion of the knee is recorded at 6, 24 and 48 h postoperatively, and also during a timed up and go (TUG) test at 24 and 48 h (see **Appendix 3**). Furthermore, highest and average pain score for 0-24 and 24-48 h are recorded.

Nausea, sedation, and dizziness are recorded on a VRS scale (none, mild, moderate, severe) at 6, 24, and 48 h. Quality of sleep is ranked on a VRS scale (very bad, fairly bad, fairly good, very good) and level of fatigue on a VRS scale (none, mild, moderate, severe) at 24 and 48 h. The number of productive vomiting events (volume estimated over 10 ml) is recorded 0–24 and 24-48 h. Total use of ondansetron and droperidol (DHB) (mg) is recorded 0–24 h and 24-48 h. Participant-reported adverse effects are recorded 0-48 h.

If participants are discharged after 24 h, but before 48 h, a telephone interview will be conducted at 48 h in order to retrieve data as stated above. Instead of TUG, participants will report pain when supporting their own weight on the knee.

Participants are given a questionnaire (checkmarks) on pain, sleep, and satisfaction with the overall pain treatment for POD 3-7 (see **Appendix 5**). Pain is recorded in the morning and in the evening including an average score for the day with NRS. Sleep is scored on a VRS scale each morning.

The 90-day mortality rate will be retrieved from the Civil Registration System, "CPR-registret", and SAEs are recorded from the Danish National Patient Registry, "Landspatientregisteret". SAEs are defined as modified SAEs. A modified SAE is defined as SAE, according to the ICH-GCP guidelines[22] excluding "prolongation of hospitalisation", as we recognise that it will be impossible to adjudicate such events.

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Permanent use of opioids 90 days after surgery will be retrieved from the Danish National Pharmaceutical Statistic Registry, "Lægemiddelstatistikregisteret".

The 90-day follow-up will be performed by telephone and mail, and the participants will fill out questionnaires on quality of life and knee function (EQ5D5L and Oxford-Knee-Score, respectively (see **Appendix 5**)). Furthermore, participants will be asked about the need for medical attention, anti-biotics, intervention, and/or re-operation.

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Appendix 2, **Definition of populations and violations**

**Intention-to-treat population**: All randomized participants who have undergone the planned total knee arthroplasty surgery

**Per protocol population**: All randomized participants who have undergone planned total knee arthroplasty surgery except participants having one or more protocol violations as defined below.

**Major protocol violations:**

- Participants not receiving allocated trial treatment
- Participants withdrawing from the trial, allowing the use of registered data
- Participants undergoing surgery (besides the TKA) OR a procedure in the intervention period

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Appendix 3, **Timed Up and Go (TUG) test**

Purpose: Assessment of participant mobility

Investigator instructions: The participant must wear firm foot ware and can use walking aid of their need. The TUG starts with the participant placed in a chair and a clear identified line on the floor 3 meters in front of the chair.

Participant instructions: "When I say WALK you will do as follows":

1. Stand up
2. Walk to the line 3 meters in front of you at your preferred pace
3. Turn 180 degrees at the line
4. Walk back to the chair at your preferred pace
5. Sit down again

Timing:

Starts at the command "walk"

Stops when the participant sits in the chair again

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Appendix 4, **Trial organisation**

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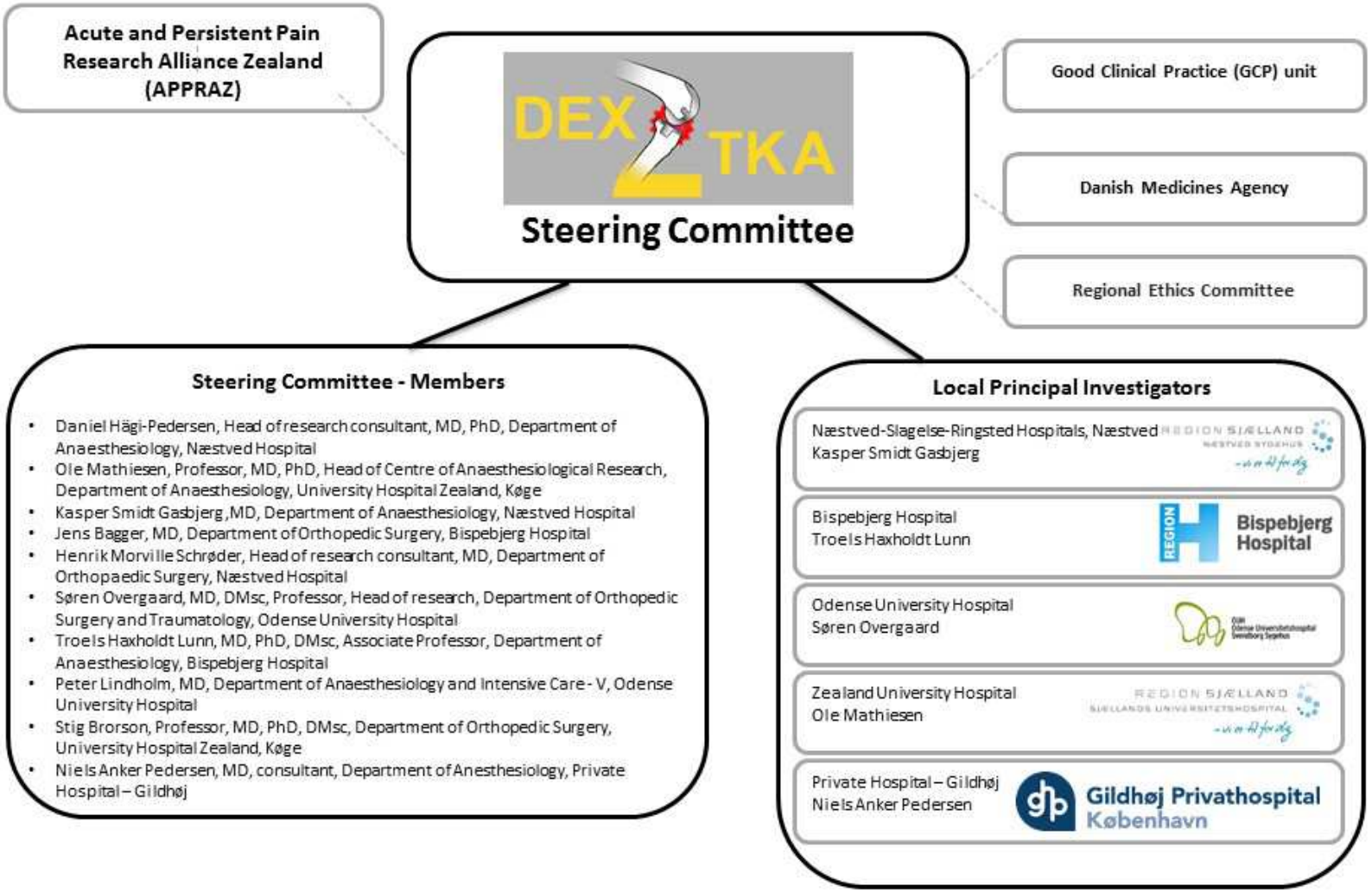
## DEX-2-TKA trial organisation



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Appendix 5, **Questionnaires (in Danish): Questionnaire postoperative day 3-7, EQ5D5L, Oxford Knee Score**

**Questionnaire postoperative day 3-7**

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DEX-2-TKA: Dexamethasone twice for pain treatment of total knee arthroplasty
A randomized blinded placebo-controlled clinical trial

EudraCT number: 2018-001099-39

# Dagbog

## i forbindelse med deltagelse i


## 3.-7. dag efter operation

**Navn:**

**CPR-NR:**

**Operationsdato:**

DEX-2-TKA: Dexamethasone twice for pain treatment of total knee arthroplasty
A randomized blinded placebo-controlled clinical trial

EudraCT number: 2018-001099-39

### 3. dag efter operation

**Hvordan er din smerter her til morgen – sæt et kryds:**

0 1 2 3 4 5 6 7 8 9 10
Ingen smerte — Værst tænkelig smerte

**Hvorledes vil du rangere din søvn – sæt et kryds?**

☐ Meget god ☐ Rimelig god ☐ Rimelig dårlig ☐ Meget dårlig

**Var din søvn forstyrret – sæt kryds:** ☐ Nej ☐ Ja

**Hvis ja – hvad bestod forstyrrelsen af – sæt et eller flere kryds:**

☐ Smerte ☐ Kvalme ☐ Opkast ☐ Uro ☐ Forstyrrelse udefra ☐ Anden årsag

**AFTEN**

**Hvordan er dine smerter her ved sengetid – sæt et kryds:**

0 1 2 3 4 5 6 7 8 9 10
Ingen smerte — Værst tænkelig smerte

**Hvordan har dine smerter været i løbet af dagen – sæt et kryds som udtryk for gennemsnittet:**

0 1 2 3 4 5 6 7 8 9 10
Ingen smerte — Værst tænkelig smerte

DEX-2-TKA: Dexamethasone twice for pain treatment of total knee arthroplasty
A randomized blinded placebo-controlled clinical trial

EudraCT number: 2018-001099-39

### 4. dag efter operation

**Hvordan er dine smerter her til morgen – sæt et kryds:**

0 1 2 3 4 5 6 7 8 9 10
Ingen smerte — Værst tænkelig smerte

**Hvorledes vil du rangere din søvn – sæt et kryds?**

☐ Meget god ☐ Rimelig god ☐ Rimelig dårlig ☐ Meget dårlig

**Var din søvn forstyrret – sæt kryds:** ☐ Nej ☐ Ja

**Hvis ja – hvad bestod forstyrrelsen af – sæt et eller flere kryds:**

☐ Smerte ☐ Kvalme ☐ Opkast ☐ Uro ☐ Forstyrrelse udefra ☐ Anden årsag

**AFTEN**

**Hvordan er dine smerter her ved sengetid – sæt et kryds:**

0 1 2 3 4 5 6 7 8 9 10
Ingen smerte — Værst tænkelig smerte

**Hvordan har dine smerter været i løbet af dagen – sæt et kryds som udtryk for gennemsnittet:**

0 1 2 3 4 5 6 7 8 9 10
Ingen smerte — Værst tænkelig smerte

DEX-2-TKA: Dexamethasone twice for pain treatment of total knee arthroplasty
A randomized blinded placebo-controlled clinical trial

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### 5. dag efter operation

**Hvordan er dine smerter her til morgen – sæt et kryds:**

0 1 2 3 4 5 6 7 8 9 10
Ingen smerte — Værst tænkelig smerte

**Hvorledes vil du rangere din søvn – sæt et kryds?**

☐ Meget god ☐ Rimelig god ☐ Rimelig dårlig ☐ Meget dårlig

**Var din søvn forstyrret – sæt kryds:** ☐ Nej ☐ Ja

**Hvis ja – hvad bestod forstyrrelsen af – sæt et eller flere kryds:**

☐ Smerte ☐ Kvalme ☐ Opkast ☐ Uro ☐ Forstyrrelse udefra ☐ Anden årsag

**AFTEN**

**Hvordan er dine smerter her ved sengetid – sæt et kryds:**

0 1 2 3 4 5 6 7 8 9 10
Ingen smerte — Værst tænkelig smerte

**Hvordan har dine smerter været i løbet af dagen – sæt et kryds som udtryk for gennemsnittet:**

0 1 2 3 4 5 6 7 8 9 10
Ingen smerte — Værst tænkelig smerte

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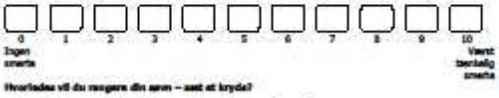
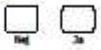
## 6. dag efter operation

**Hvordan er dine smerter her til morgen – sæt et kryds:**

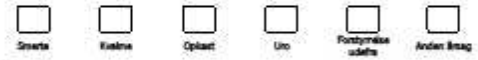



**Hvorledes vil du rangere din søvn – sæt et kryds?**


**Var din søvn forstyrret – sæt kryds:**




**Hvis ja – hvad bestod forstyrrelsen af – sæt et eller flere kryds:**




## AFTEN

**Hvordan er dine smerter her ved sengetid – sæt et kryds:**


**Hvordan har dine smerter været i løbet af dagen – sæt et kryds som udtryk for gennemsnittet:**


DEX-2-TKA: Dexamethasone twice for pain treatment of total knee arthroplasty
A randomized blinded placebo-controlled clinical trial

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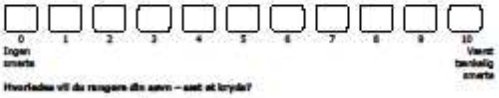
## 7. dag efter operation (husk sidste side)

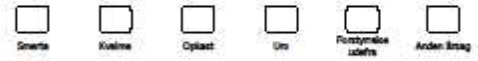
**Hvordan er dine smerter her til morgen – sæt et kryds:**




**Hvorledes vil du rangere din søvn – sæt et kryds?**

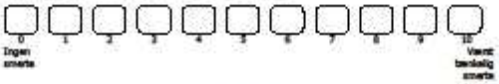

**Var din søvn forstyrret – sæt kryds:**


**Hvis ja – hvad bestod forstyrrelsen af – sæt et eller flere kryds:**

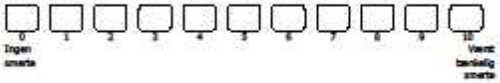



## AFTEN

**Hvordan er dine smerter her ved sengetid – sæt et kryds:**




**Hvordan har dine smerter været i løbet af dagen – sæt et kryds som udtryk for gennemsnittet:**




DEX-2-TKA: Dexamethasone twice for pain treatment of total knee arthroplasty
A randomized blinded placebo-controlled clinical trial

EudraCT number: 2018-001099-39

## Overordnet tilfredshed med den smertestillende behandling du har fået med hjem fra hospitalet.

**Hvorledes vil du rangere den smertestillende behandling du har modtaget– sæt et kryds?**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EQ-5D-5L

Helbredsspørgeskema

Dansk version for Danmark

*(Danish version for Denmark)*

Developed by the EuroQol Group

Under hver overskrift bedes du sætte kryds i DEN boks, der bedst beskriver dit helbred I DAG.

**BEVÆGELIGHED**

- Jeg har ingen problemer med at gå omkring ☐
- Jeg har lidt problemer med at gå omkring ☐
- Jeg har moderate problemer med at gå omkring ☐
- Jeg har store problemer med at gå omkring ☐
- Jeg kan ikke gå omkring ☐

**PERSONLIG PLEJE**

- Jeg har ingen problemer med at vaske mig eller klæde mig på ☐
- Jeg har lidt problemer med at vaske mig eller klæde mig på ☐
- Jeg har moderate problemer med at vaske mig eller klæde mig på ☐
- Jeg har store problemer med at vaske mig eller klæde mig på ☐
- Jeg kan ikke vaske mig eller klæde mig på ☐

**SÆDVANLIGE AKTIVITETER** *(fx. arbejde, studie, husarbejde, familie- eller fritidsaktiviteter)*

- Jeg har ingen problemer med at udføre mine sædvanlige aktiviteter ☐
- Jeg har lidt problemer med at udføre mine sædvanlige aktiviteter ☐
- Jeg har moderate problemer med at udføre mine sædvanlige aktiviteter ☐
- Jeg har store problemer med at udføre mine sædvanlige aktiviteter ☐
- Jeg kan ikke udføre mine sædvanlige aktiviteter ☐

**SMERTER / UBEHAG**

- Jeg har ingen smerter eller ubehag ☐
- Jeg har lidt smerter eller ubehag ☐
- Jeg har moderate smerter eller ubehag ☐
- Jeg har stærke smerter eller ubehag ☐
- Jeg har ekstreme smerter eller ubehag ☐

**ANGST / DEPRESSION**

- Jeg er ikke angstslig eller deprimeret ☐
- Jeg er lidt angstslig eller deprimeret ☐
- Jeg er moderat angstslig eller deprimeret ☐
- Jeg er meget angstslig eller deprimeret ☐
- Jeg er ekstremt angstslig eller deprimeret ☐



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- Vi vil gerne vide, hvor godt eller dårligt dit helbred er I DAG.
- Denne skala er nummereret fra 0 til 100.
- 100 svarer til det bedste helbred, du kan forestille dig. 0 svarer til det dårligste helbred, du kan forestille dig.
- Sæt et X på det sted på skalaen, der viser, hvordan dit helbred er I DAG.
- Skriv derefter det tal, du har markeret på skalaen, ind i boksen nedenunder.

DIT HELBRED I DAG = ☐




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**Oxford Knee Score**

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**Sådan udfyldes Oxford Knæ Score (OKS):**

Læs teksten/vejledningen på spørgeskemaet.

- Du skal svare på alle spørgsmål i forhold til, hvad der bedst beskriver, hvordan du har haft det i løbet af de sidste fire uger.
- Hvis der er spørgsmål, hvor dit svar ikke helt passer til svarmulighederne, skal du sætte kryds ved det svar, der passer bedst til din situation.
- Der skal kun sættes ét kryds per spørgsmål.
- Det er vigtigt for undersøgelsen, at alle spørgsmålene besvares.
- Det er vigtigt at bruge en kuglepen, der skriver mørkeblåt eller en anden mørk farve, når skemaet udfyldes.
- Kryds skal være nemme at tolke, som vist i nedenstående eksempler.

Eksempler på angivelser af afkrydsning

| | Rigtigt | Forkert |
|---|---|---|
| Sæt tydeligt kryds indenfor feltet. Kryds må ikke nærme kanten rundt om feltet | ☒ | ☒ |
| Hvis et felt er udfyldt forkert, skal HELE feltet sværtes, og krydset sættes i det rigtige felt | ■ | ☒ |





CPR. NR.:

**Når du ser tilbage på de sidste 4 uger ... (Kun ét kryds per spørgsmål)**

**1. Hvordan vil du beskrive de smerter, som har haft i knæet?**

| 1. Ingen smerter | 2. Meget lette smerter | 3. Lette smerter | 4. Moderate smerter | 5. Stærke Smerter |
|---|---|---|---|---|
| ☐ | ☐ | ☐ | ☐ | ☐ |

**2. Har du haft problemer med at vaske og tørre dig (over det hele) på grund af dit knæ?**

| 1. Nej, slet ingen problemer | 2. Meget lidt besvær | 3. Ja, moderat besvær | 4. Ja, meget store Problemer | 5. Det er helt umuligt |
|---|---|---|---|---|
| ☐ | ☐ | ☐ | ☐ | ☐ |

**3. Har du haft problemer med at komme ind i eller ud af en bil eller bruge offentlig transport på grund af dit knæ?**

| 1. Nej, slet ingen problemer | 2. Meget lidt besvær | 3. Ja, moderat besvær | 4. Ja, meget store problemer | 5. Det er helt umuligt |
|---|---|---|---|---|
| ☐ | ☐ | ☐ | ☐ | ☐ |

**4. Hvor lang tid kan du gå, før du har fået stærke smerter i knæet (med eller uden stok)?**

| 1. Ingen smerter/kan gå mere end 30 minutter | 2. 16 til 30 minutter | 3. 5 til 15 minutter | 4. Kun meget korte afstande | 5. Det er helt umuligt at gå |
|---|---|---|---|---|
| ☐ | ☐ | ☐ | ☐ | ☐ |





**Når du ser tilbage på de sidste 4 uger ... (Kun ét kryds per spørgsmål)**

**5. Hvor stærke smerter har du haft i knæet, når du har skullet rejse dig op efter at have siddet med (f.eks. ved middagsbordet)?**

| 1. Slet ingen smerter | 2. Lette smerter | 3. Moderate smerter | 4. Stærke smerter | 5. Uudholdelige smerter |
|---|---|---|---|---|
| ☐ | ☐ | ☐ | ☐ | ☐ |

**6. Har du haltet på grund af dit knæ?**

| 1. Sjældent/aldrig | 2. Sommetider eller kun når ben begynder at gå | 3. Ja, en del af tiden eller kun når ben begynder at gå | 4. Ja, det meste af tiden | 5. Ja, hele tiden |
|---|---|---|---|---|
| ☐ | ☐ | ☐ | ☐ | ☐ |

**7. Har du kunnet gå ned på knæ og rejse dig op igen?**

| 1. Ja, nemt | 2. Næsten uden besvær | 3. Med moderat besvær | 4. Med meget stort besvær | 5. Nej, umuligt |
|---|---|---|---|---|
| ☐ | ☐ | ☐ | ☐ | ☐ |

**8. Har du været plaget af smerter i knæet, når du ligger i sengen om natten?**

| 1. Nej, ikke på noget tidspunkt | 2. Kun en enkelt nat eller to | 3. Nogle nætter | 4. De fleste nætter | 5. Hver nat |
|---|---|---|---|---|
| ☐ | ☐ | ☐ | ☐ | ☐ |





**Når du ser tilbage på de sidste 4 uger ... (Kun ét kryds per spørgsmål)**

**9. I hvor høj grad har smerter i knæet besværliggjort dit sædvanlige arbejde (inkl. husarbejde)?**

| 1. Slet ikke | 2. En lille smule | 3. En del | 4. Meget | 5. Umuligt at arbejde |
|---|---|---|---|---|
| ☐ | ☐ | ☐ | ☐ | ☐ |

**10. Har du følt, at dit knæ pludselig kunne give efter eller svigte?**

| 1. Sjældent/aldrig | 2. Sommetider eller kun når jeg rejser mig | 3. Ofte, ikke kun når jeg rejser mig | 4. Det meste af tiden | 5. Hele tiden |
|---|---|---|---|---|
| ☐ | ☐ | ☐ | ☐ | ☐ |

**11. Har du selv kunnet stå helt i ro?**

| 1. Ja, nemt | 2. Næsten uden besvær | 3. Med moderat besvær | 4. Med meget stort besvær | 5. Nej, det har været umuligt |
|---|---|---|---|---|
| ☐ | ☐ | ☐ | ☐ | ☐ |

**12. Har du kunnet gå ned ad trapper?**

| 1. Ja, nemt | 2. Næsten uden besvær | 3. Med moderat besvær | 4. Med meget stort besvær | 5. Nej, det har været umuligt |
|---|---|---|---|---|
| ☐ | ☐ | ☐ | ☐ | ☐ |



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