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The effect of Music on Clinical outcome after Hip fracture OPeratIoNs (MCHOPIN): study protocol of a multicentre randomised controlled trial

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Disclosures

None

Strengths and limitations of this study

- This multicentre randomised controlled trial will investigate the effects of perioperative recorded music on delirium and postoperative recovery in elderly proximal femur fracture patients.
- Due to the profound effects of delirium on patient outcome and recovery, delirium prevention is a quality indicator in health care for many hospitals worldwide.
- Perioperative recorded music has significant beneficial effects on eliciting factors of delirium.
- Results of this trial will give additional insight in reducing postoperative delirium, as well as the relation between the neurohormonal cortisol stress response to surgery, delirium occurrence and postoperative complication rate.
- Limitations due to lack of blinding related to the music intervention can be justified, as surgical studies and studies evaluating delirium with non-pharmacological interventions can often not be blinded in general.

ABSTRACT

Background: Patients undergoing proximal femur fracture surgery are at high risk for postoperative complications, with postoperative delirium occurring in 25-40% of patients. Delirium has profound effects on patient outcome and recovery, the patient's family, caregivers, and medical costs. Perioperative music has a beneficial effect on eliciting, modifiable risk factors of delirium. Therefore, the aim of this trial is to evaluate the effect of perioperative recorded music on postoperative delirium in proximal femur fracture patients undergoing surgery.

Methods and analysis: The MCHOPIN study is an investigator-initiated, multicentre, randomised controlled, open-label, clinical trial. Five hundred and eight proximal femur fracture patients meeting eligibility criteria will be randomised to the music intervention or control group with concealed allocation in a 1:1 ratio, stratified by hospital site. The perioperative music intervention consists of preselected lists totalling 30 hours of music, allowing participants to choose their preferred music from these lists (classical, jazz and blues, pop, Dutch). The primary outcome measure is postoperative delirium rate. Secondary outcome measures include pain, anxiety, medication requirement, postoperative complications, hospital length of stay, and 30-day mortality. A 90-day follow-up will be performed in order to assess nursing home length of stay, readmission rate and functional ability to perform daily living activities. Furthermore, the cost and cost-effectiveness of the music intervention will be assessed. Data will be analysed according to an intention-to-treat principle.

Ethics and dissemination: The study protocol has been approved by the Medical Research Ethics Committee Erasmus MC on October 8, 2018 (MEC-2018-110; NL64721.078.18). The trial will be carried out following the Declaration of Helsinki principles, Good Clinical Practice guidelines and Dutch Medical Research Involving Human Subjects Act. Research data will be reported following CONSORT guidelines and study results will be published in a peer-reviewed journal.

Registration details: Dutch Trial Register (NTR7036).

Abbreviations

ASA, American Society of Anesthesiologists; AVG, Dutch Personal Data Protection Regulation (in Dutch: Algemene Verordening Gegevensbescherming); DOS, Delirium Observation Screening; DSM-IV criteria, Diagnostic Statistical Manual-IV criteria; ERAS, Enhanced Recovery After Surgery; IGZ, Dutch Health Care Inspectorate (in Dutch: Inspectie voor de Gezondheidszorg); Katz-ADL6, Katz Index of Activities of Daily Living; ME, Morphine Equivalent (1 mg ME = 1 mg of parenteral morphine; mg milligram; MMSE, Mini-Mental State Examination; NRS, Numeric Rating Scale; STAI, State Trait Anxiety Inventory; STAI-6, State Trait Anxiety Inventory-6; WMO, Medical Research Involving Human Subjects Act (in Dutch: Wet Medisch wetenschappelijk Onderzoek met Mensen).

INTRODUCTION

Proximal femur fractures are common in the elderly and are primarily treated surgically.[1] These frail patients are at a high risk for the occurrence of postoperative complications, as they often have significant comorbidity with polypharmacy use.[2] A prevalent in-hospital complication of the elderly is delirium, an acute, fluctuating, cognitive and consciousness disorder.[3] Postoperative delirium rates in elderly Dutch proximal femur fracture surgery patients have been observed to vary between 25 to 40%.[4 5] It has been associated with an increased rate of additional postoperative complications,[6] a prolonged length of hospital stay,[6 7] and higher medical costs[7]. Moreover, it has a thorough impact on the patient's family,[8 9] increasing the risk of poor long-term functional recovery and mortality rate.[10-12]

As the consequences of experiencing an episode of delirium are profound, delirium is nowadays regarded as a state of acute brain dysfunction.[13] Therefore, there is an increasing interest in delirium prevention and reduction. The exact pathophysiological mechanism of delirium is multifactorial and complex. Primary prevention with non-pharmacological interventions is generally regarded as the most accepted and effective treatment strategy,[3 14] especially since conflicting reports on the effectiveness of prophylactic drug use to prevent delirium have been reported.[15-17] Multiple modifiable precipitating risk factors have been identified.[3 18] These include increased postoperative pain levels,[19-21] higher opioid, sedative and benzodiazepine medication dosages,[21-23] as well as a more vigorous physiological stress response to surgery and elevated stress hormone cortisol level.[3 24] Current patient care aims to reduce these risk factors in order to prevent delirium.

Perioperative recorded music as a non-pharmacological intervention can reduce postoperative pain,[25] intraoperative sedative and postoperative opioid medication requirement,[26] and attenuate the physiological stress response to surgery.[26] Comparisons have been drawn with the most well-known non-pharmacological interventions for surgery, collectively known as

the Enhanced Recovery After Surgery (ERAS) protocols, which have the same objectives.[27] Moreover, the music intervention seems to be well-liked by patients, with high patient satisfaction levels and willingness to listen to perioperative music again if they were to undergo surgery in the future.[26] The effects of perioperative music on postoperative complications, patient outcome, and recovery have only sparingly been investigated,[26 28] with most studies focusing on postoperative pain levels, anxiety or medication requirement in the first few days after surgery. To date, only four small studies in elective knee and hip replacement surgery with sample sizes of 60 patients or less examined the effect of music on confusion and cognitive functioning in adult surgical patients.[29-31] Only two used a delirium screening tool,[32 33] but positive results were reported in all studies.

This multicentre randomised controlled trial will investigate whether perioperative music can reduce the occurrence of postoperative delirium in elderly proximal femur fracture patients undergoing surgery. Secondary objectives are to assess the effects of perioperative music on pain, anxiety, medication use, postoperative complications, neurohormonal stress response, hospital length of stay, nursing home length of stay, 30-day mortality, 90-day readmission, 90-day functional ability to perform daily living activities, costs, and cost-effectiveness.

METHODS AND ANALYSIS

Trial design and setting

The MCHOPIN study is an investigator-initiated, multicentre, randomised controlled, open-label, clinical trial. Proximal femur fracture patients meeting eligibility criteria will be randomised to the music intervention or control group using a secure web-based, computerized randomisation system with concealed allocation in a 1:1 ratio, stratified by hospital site. Only study staff members and their delegates will have login credentials. The randomisation code for allocation will be kept concealed from the study staff recruiting patients. The music group will receive recorded music as an intervention before, during and after surgery, whilst the control group will not but will wear headphones without music during surgery instead. The study will take place in four non-academic hospitals and one academic hospital. Patients will be followed until 90 days after the proximal femur fracture surgical procedure.

Eligibility, recruitment and consent

Potential eligible patients will be informed about the MCHOPIN study while in the emergency department or upon admission to the surgical ward. Information will be provided verbally as well as on paper through a patient information folder with an informed consent form. Patients meeting eligibility criteria and willing to participate will be randomised after written informed consent obtainment. In general, proximal femur fracture patients will be operated within 48 hours of hospital admission based on guidelines set by the Dutch Health Care Inspectorate (in Dutch: Inspectie voor de Gezondheidszorg (IGZ)). Therefore, it is not possible to give patients more than a day to consider participation. However, the intervention is non-invasive and not associated with any risks or adverse events[26]. As beneficial effects of music on disruptive behaviour and cognition in dementia patients have been reported[34], proximal femur fracture surgery patients with dementia are not excluded from study participation, although written

informed consent by the proxy is necessary. Patients with hearing aids can also readily participate, which has been consulted with the Erasmus MC auditory centre.

Inclusion criteria:

1. Patients with a proximal femur fracture undergoing surgical treatment
2. Age ≥ 65 years old
3. Provision of written informed consent by patient or proxy

Exclusion criteria

1. Additional serious injuries or additional surgical procedures that may affect any of the outcome parameters
2. Simultaneous bilateral hip fracture
3. Implant in situ in the affected hip
4. Severe hearing impairment, defined as no verbal communication possible
5. Patients unwilling or unable to comply with the intervention
6. Preoperative planned hospital discharge and return to nursing home within 48 hours of admission
7. Insufficient knowledge of the Dutch or English language to understand the study documents in the judgement of the attending physician or researcher
8. Participation in another intervention study that might influence the duration of surgery or any of the outcome parameters

Primary outcome

The primary outcome measure is postoperative delirium. Participating patients will be screened using the Delirium Observation Screening (DOS) scale, a diagnostic nursing screening tool. The

DOS scale is a 13-item scale facilitated in order to recognize delirium early, with valid consistency and reliability in both geriatric patients and elderly hip fracture patients.[35 36] The DOS end score is the sum of the three DOS scales, assessed during each shift by the nurse, divided by 3. A DOS end score ranges between 0 and 13. In a study of 92 hip fracture patients, a DOS end score of 3 or more had a 94.4% sensitivity of delirium, while a score less than 3 had a 76.6% specificity.[35 36] Because the DOS scale is easy in use, requires no active patient participation and has been validated in several trials,[37 38] it is a standard part of multidisciplinary delirium prevention measures in proximal femur fracture patients in the Dutch National Guidelines on delirium. In case of a DOS end score of 3 or more, the geriatrician will be consulted for patient assessment to confirm clinical diagnosis of delirium using the Diagnostic Statistical Manual-IV (DSM-IV) criteria. These criteria define delirium as an acute, fluctuating disturbance of consciousness with inability to focus and shift of attention, caused by a general medical condition. In all participating hospitals, a geriatrician is part of and actively involved in the proximal femur fracture surgery patient care team.

Secondary outcomes

Secondary outcome measures are:

- Postoperative pain, assessed using an 11-point numeric rating scale (NRS), in which 0 implies no pain and 10 implies the worst pain possible.
- Anxiety, assessed using the State-Trait Anxiety Inventory-6 (STAI-6).[39] Feelings of anxiety are reported on a four-point Likert scale for each item, with a score between 20 and 80 points for each questionnaire. Scoring is achieved by reverse scoring the 3 positive items, sum all 6 scores, and multiply the total score by 20/6. A higher score correlates to a higher level of anxiety. The State-Trait Anxiety Inventory (STAI), consisting of two 20-item subscale questionnaires, is one of the most frequently used anxiety questionnaires in clinical research.[40] The state subscale measures situation

related anxiety, anxiety at the very moment, while the trait subscale measures disposition related anxiety, anxiety as a general personal characteristic trait). A major drawback of the STAI is its length, especially in a study population of elderly patients with frequent cognitive impairment, pain and opioid requirement. In order to increase compliance and minimize unanswered items, the 6-item short form of the STAI-state by Marteau and Bekker (1992) will be used.[39] The STAI-6 has a high internal reliability and correlation with the full-form STAI,[39 41 42] has been used in clinical research in elderly patients,[43 44] and has been validated in Dutch.[45]

- Medication use, consisting of intraoperative and postoperative opioid medication, as well as postoperative benzodiazepines and postoperative antipsychotic medication for the treatment of delirium. Data will be collected from the electronic patient file. Analgesic opioid medication will be converted to milligrams of morphine equivalents (1 mg ME = 1 mg parenteral morphine).
- Postoperative complication rate. Data will be collected from the electronic patient database and classified according to the Clavien-Dindo classification.[46]
- Neurohormonal stress response, assessed by measuring serum cortisol. An increased stress response after surgery has been associated with an increased risk of postoperative delirium.[24] The duration until peak cortisol level depends on the surgical severity and is an indicator of intrinsic physiological stress.[47] Peak levels of cortisol are observed 4 hours after start of surgery in moderate and after 8 hours in major surgical procedures. Proximal femur fracture surgery is generally classified as a major surgical procedure. Therefore, the second serum cortisol will be drawn 6 hours after the first sample. This will be combined with the blood draw postoperatively for the postoperative serum haemoglobin measurement, which is part of standard surgical care.
- Hospital length of stay in days, as calculated from the hospital admission date until declared ‘medically ready for discharge’ by the attending physician as recorded in the

patient's medical file. Also the full length of stay until the actual discharge from hospital will be assessed.

- 30-day mortality, as calculated from date of admission.
- Nursing home length of stay in days, as calculated from nursing home admission date until discharge.
- 90-day readmission, as calculated from date of admission.
- 90-day functional ability to perform daily living activities, which will be assessed during standard postoperative outpatient visit 3 months postoperatively using the Katz Index of Activities of Daily Living (Katz-ADL6). This 6-item instrument assesses basic activities of daily living in 6 functions, with a total score of 6 indicating full function and a score of 2 or less severe functional impairment.[48]
- Through an economic evaluation, the cost-effectiveness of the music intervention will be investigated, using the method of cost-effectiveness analysis (CEA). The evaluation will be conducted from a healthcare perspective, with a time horizon of 90 days. It will make a comparison between the intervention and the control group by identifying, measuring, and valuing the costs and patient outcomes of both treatment strategies. The costs will include costs of the initial hospital admission (either on the ward or on the intensive care unit), primary surgery and additional procedures (including surgical re-interventions), medications, diagnostic imaging, in-hospital consultations, and costs for headphones and sound equipment. The analysis will take into account costs after hospital discharge, including costs of outpatient consultations, visits to the emergency room, consultations with the general practitioner, home care, and nursing home admissions. Data on resource consumption will be collected from the electronic patient database and using a custom follow-up questionnaire. These data will then be combined with unit costs to generate patient-level costs. Costs of productivity losses will be ignored in this study, because these are expected to be minor, given the age range of the patients. Regarding

patient outcomes, the CEA will consider the occurrence of delirium (as defined above). An incremental cost-effectiveness ratio (ICER) will be calculated as the difference in cost between the two treatment strategies divided by the difference in effectiveness, unless one treatment dominates the other (i.e., has lower costs and greater effects). This ICER will be expressed as incremental costs per case of delirium prevented.

Additional study parameters assessed will be patient demographic characteristics, preoperative medication use, medical and surgical patient history, living situation prior to hospital admission, education level, injury and treatment characteristics, and music preferences and its importance in daily life. Cognitive functioning, a prominent risk factor for delirium[49], will be screened preoperatively using the Mini-Cog, a three-item screening questionnaire with high correlation to cognitive functioning assessment by the Mini-Mental State Examination (MMSE)[50 51].

Study intervention

The music group will listen to music preoperatively, intraoperatively and postoperatively during the first five days after surgery. The preoperative music intervention will be 15 minutes. The intraoperative music intervention will start after anaesthesia induction until the patient choses to remove the headphone in the recovery room. Postoperatively, the music group will listen to music twice a day for 30 minutes, starting from the first until the fifth postoperative day or until patient discharge. The control group will receive standard patient care and in addition wear headphones intraoperatively without music, in order to prevent that the potential beneficial effect of music is attributed solely to noise reduction. Previous studies have reported noise levels exceeding 100 decibels adjusted during surgery[52], with higher noise levels reportedly increasing postoperative complications rate and stress hormone levels[53-55].

The music intervention consists of preselected music divided in four playlists (classical, jazz and blues, pop, and Dutch music) providing approximately 30 hours of music using a tablet.

Patients are allowed to choose music from these list, as the largest beneficial effects were previously observed when patients selected music from a preselected playlist[25]. Moreover, it is unlikely that the elderly proximal femur fracture surgery patients admitted through the emergency department will bring their own favourite music. Music was selected by a panel of five research physicians with extensive knowledge of perioperative music, based on literature recommendations and music used in previous studies. Care was taken to choose popular music from the patients' youth and early adulthood (50's to 80's) which would likely be familiar to the patient, as a familiar environment can reduce the occurrence of delirium[56]. Consent was obtained from the music copyright managing organizations in the Netherlands, Buma Association and Stemra Foundation (Dutch: Vereniging Buma and Stichting Stemra), to use recorded music for study research purposes.

Study procedures

A timeline detailing study procedures and outcome measures is presented in Figure 1. After signing informed consent and computerized randomisation, the Mini-Cog will be administered and baseline NRS for pain and STAI-6 will be filled out also by all participants, followed by preoperative geriatric consult and DOS scores as part of standard care. A custom-made demographic questionnaire on preoperative living situation, education level and music will be provided as well.

The preoperative music intervention for the music group will start from the surgical ward when the patient is called up for surgery and continue until arrival in the operating room, whereas the control group will receive standard care preoperatively. The anaesthesiologist and surgical team will be free to decide whether general or locoregional anaesthesia will be used, as well as the anaesthesia regimen. Preferably, anaesthesia administration will be guided by using a bispectral index monitor or comparable anaesthesia depth monitoring device. After induction, the first cortisol blood sample will be drawn and all subjects will receive headphones. The

control group will wear headphones in order to assess the music intervention and not noise reduction. All participants will wear headphones until arrival in the recovery room, where they can chose to remove them when they wish. No corticosteroids will be administered between the first and second cortisol blood sample drawing (6 hours after the first blood sample), unless this is deemed clinically necessary by the patient care team. As previously mentioned, cortisol will not be assessed in a selected group of patients participating in his trial.

For all participating patients postoperatively, the DOS will be assessed thrice daily, with the geriatrician actively involved in proximal femur fracture surgery patient care. The NRS for pain will be assessed daily and postoperative opioid dosage will be administered based on the NRS and care team observations. The STAI-6 will be filled out by all participants during the first and second postoperative day. Data on the NRS for pain, DOS, postoperative medication requirement, postoperative complication rate, hospital length of stay and 30-day mortality rate will be retrieved from the electronic patient database. All participants will be followed until three months postoperatively. Two questionnaires, the custom-made follow-up questionnaire and the Katz-ADL6 questionnaire, will be administered during either the outpatient follow-up visit or by phone. The follow-up questionnaire will assess nursing home length of stay, 90-day readmission rate, and information needed for the economic evaluation.

Sample size calculation

Literature on the frequency of postoperative delirium in proximal femur fracture surgery patients varies between 15 and 60 percent,[2] with a recent meta-analysis reporting an accumulated prevalence of 24 percent.[57] Delirium in Dutch proximal femur fracture surgery patients over 65 years of age has been observed in 19 to 37 percent of patients.[58 59] Previously, a meta-analysis assessing effectiveness of different, mostly non-pharmacological interventions reported a reduction in delirium rates of 13%.[60] In order to assess a minimally clinical relevant reduction of 13% in delirium frequency when taking 15-60% of delirium into account, with a power of 80%,

alpha of 5% and planned two-sided testing, taking into account possible in-hospital mortality and loss-to-follow-up of 10% overall, 508 patients should be enrolled (254 per group).

Data collection and management

Clinical research assistants will be available at participating hospital sites to assist in executing study procedures and data collection. Research data will be collected using questionnaires and with a case report forms with data from the electronic patient database. The handling of personal data will comply with the Dutch Personal Data Protection Regulation (in Dutch: Algemene Verordening Gegevensbescherming, AVG). Research data will be stored electronically in a database with an audit trail that meets Good Clinical Practice standards (OpenClinica) and will be handled confidentially. Any information on paper collected during this study will be placed in a research folder, which will be filed in locked cabinets in research offices at the participating hospitals. Data will be stored during the study period and for a period of 15 years after completion of the study.

Monitoring, safety and auditing

An appointed monitor will develop standard procedures and details on the monitoring activities. The sponsor/investigator has a liability insurance which is in accordance with the Medical Research Involving Human Subjects Act (in Dutch: Wet Medisch wetenschappelijk Onderzoek met Mensen, WMO). The Medical Research Ethics Committee Erasmus MC has given dispensation from the statutory obligation to provide insurance for subjects participating in medical research, as participation in this study is considered to be without risks.

No deleterious or negative adverse side-effects associated with listening to music as a perioperative intervention are known[26]. In accordance, the investigator will report all serious adverse events to the sponsor, except for the specific serious adverse events which are considered not related to the music intervention and common in proximal femur fracture surgery

patients. A maximum sound level will be ensured to prevent hearing damage. The headphones and sound equipment will be cleaned with a damp microfiber cloth and the ear pads or buds replaced after use by a patient during hospital stay, in order to reuse the devices, in accordance with the Erasmus MC Infection Prevention Unit and local hospital protocols. No additional or enhanced hygiene measures will be needed concerning the use of headphones and sound equipment in the operating room complex and the same sound equipment set will be used on the ward.

Statistical analysis

Data will be analysed using the Statistical Package for the Social Sciences (SPSS) version 24.0 or higher (SPSS, Chicago, Ill., USA). Normality of continuous data will be tested with the Shapiro-Wilk test. Homogeneity of variances will be tested using the Levene's test. A two-sided p-value <0.05 will be taken as threshold of statistical significance in all statistical tests. The analyses will be performed on an intention to treat basis. Should there be 5% crossovers, a per protocol analysis will also be done. If necessary, missing values will be replaced using multiple imputations following the predictive mean matching method, using ten imputations.

Descriptive analysis will be performed in order to report the outcome measures for both treatment groups. For continuous data, the mean and SD (parametric data) or the median and percentiles (non-parametric data) will be reported per treatment group. For categorical data, numbers and frequencies will be reported per treatment group. The only exception is that costs will be reported as mean with 95% confidence interval (95% CI). The 95% CI around the mean costs will be approximated by nonparametric bootstrapping. Continuous data will be tested using the Student's T-test or the Mann-Whitney U-test, as appropriate. Categorical data will be tested using the Chi-squared or Fisher's Exact test, as applicable. Both univariable and multivariable analysis will be performed. A binary logistic regression model (for binary outcomes) or multivariable linear regression model (for continuous outcomes) will be developed,

with the outcome as dependent variable and the study group (i.e., intervention or control) as covariate. Patient, injury, and treatment variables that differ between the groups and may confound the association of the intervention and outcome will be entered into the model. Variables will be entered into the model if univariate analysis produces a p-value of 0.05 or lower. The unadjusted and adjusted odds ratio's (for binary outcomes) and beta values (for continuous outcomes) will be reported with 95% confidence interval. A subanalysis for all outcome measures will be performed by stratifying patients according to their age (<80 and ≥ 80 years).

Blinding

Patients enrolled in the MCHOPIN study will not be blinded to the music intervention. While the surgical team will be blinded intraoperatively on paper as all patients will wear headphones during surgery, in practice it will not be possible to blind the surgical team as patients can adjust the music volume or ask for a different playlist whilst in the operating room or postoperatively on the surgical ward. The clinical chemist and laboratory site concerned with the analysis of the neurohormonal cortisol stress response samples will be blinded to the intervention. Also, a part of the statistical analysis, which includes the primary and almost all of the secondary outcome measures except the economic analysis, will be performed by a statistician blinded to the music intervention.

ETHICS AND DISSEMINATION

This study will be conducted in accordance to the principles of the Declaration of Helsinki (64th WMA General Assembly, Fortaleza, Brazil, 2013) and in accordance to the Medical Research Involving Human Subjects Act (in Dutch: WMO). Written informed consent will be obtained from each patient or proxy.

Ethics approval and trial registration

Approval by the Medical Research Ethics Committee Erasmus MC was obtained on October 8, 2018 (MEC-2018-110; NL64721.078.18). Local approval in the participating hospitals followed suite and the study was open for inclusion starting from March 5, 2019. The trial protocol has had no substantial amendments to the original protocol. This trial has been registered in the Dutch Trial Register (NTR7036).

Dissemination policy

Research data will be reported following the Consolidated Standards of Reporting Trials (CONSORT) guidelines[61]. No research data that can be traced to individual persons will be presented or published. On completion of the trial, the research team aims to publish the manuscript in a peer-reviewed journal and present results in national and international conferences. Each participating hospital will be invited to provide co-authors for a collaborator group authorship, consisting of one trauma surgeon and one anaesthesiologist, provided that 15 percent of the total required study sample size is included at that site. All participating hospitals will be acknowledged for their participation.

DISCUSSION

Delirium is a prevalent complication in in-hospital elderly patients and is associated with prolonged hospitalisation due to an increased risk of postoperative complications and mortality. It also leads to long-term cognitive and functional impairment[3 6 7 10 11]. Therefore, an increasing research interest in delirium prevention and treatment has developed over the past two decades. Delirium prevention is currently a health care quality indicator in many countries worldwide[62]. Several non-pharmacological multimodal intervention programs have reported beneficial results on reducing delirium[3 16], especially since the pharmacological prevention and treatment of delirium remains somewhat controversial[3 16 17 63]. Given the multifactorial factors involved in delirium development, current guidelines consist of both multimodal pharmacological and non-pharmacological interventions. While no clinical useful biomarker for delirium has currently been identified yet[64], serum cortisol reportedly has delirious effects when increased[65-68]. It has been theorized that overstimulation of the hippocampus, rich in glucocorticoid receptors and therefore susceptible for cortisol and stress, plays a role in delirium development[69]. Given that perioperative music can attenuate the neurohormonal cortisol stress response[26], combined with the significant beneficial effects of perioperative music on postoperative pain, anxiety, intraoperative sedative requirement and postoperative opioid usage[25 26], the multicentre, randomised controlled, clinical MCHOPIN trial will assess the effect of perioperative recorded music on postoperative delirium, patient outcome and recovery in elderly proximal femur fracture surgery patients.

An exhaustive literature search with a biomedical information specialist was performed on October 16th, 2020 in order to assess current literature on perioperative music and postoperative delirium in adult surgical patients. Only four randomised controlled trials evaluated the effect of music on postoperative cognitive functioning and delirium. McCaffrey and Locsin *et al.* reported significant lower acute confusion episodes in two trials with 190 elderly patients

undergoing elective hip or knee surgery[30 31]. However, confusion was ascertained by reading the nurse's narrative notes without use of screening tools for delirium recognition. Two other studies observed significantly lower rates of postoperative acute confusion ascertained using the validated NEECHAM Acute Confusion Scale when patients listened to music postoperatively compared to standard care. Sample sizes were relatively small, with only 22 and 60 elective hip and knee surgery patients included[32 33].

In the MCHOPIN study, the DOS score will be used to pro-actively screen for delirium in all participants during each nursing shift[35 37]. Given that delirium is often not recognized or misdiagnosed, a strong point of this trial is that all participating hospitals are high volume centres which actively involve the geriatrician in the care of all admitted proximal femur fracture surgery patients. Both patients and practitioners will not be blinded, as the beneficial effects of perioperative music seem largest when music is applied before, during and after surgery instead of only intraoperatively during general anaesthesia[25 26]. Also, a significant portion of proximal femur fracture surgery patients is operated on while receiving locoregional anaesthesia. We believe it acceptable that no blinding is applied, as patients cannot be blinded in many surgical trials. Only 3 and 37% of practitioners and patients were blinded in high impact surgical randomised controlled trials[70]. Moreover, primary prevention of delirium is generally accepted to be most effective with non-pharmacological interventions[3], meaning blinding is not possible. The anaesthesiologist and surgical team will be free to decide the manner of anaesthesia and perioperative analgesia regimen. Given the number of patients that will be enrolled in this trial and the stratification per hospital site, it is assumed that this will balance itself out and no differences in locoregional or general anaesthesia and analgesia medication will be observed between the intervention and the control group.

To our knowledge, this is the first large, multicentre, randomised controlled trial investigating the effect of perioperative recorded music on postoperative clinical patient outcome and recovery which also employs a reasonable follow-up time after patient discharge.

Moreover, only a limited number of studies evaluating perioperative music involved acute care or elderly surgical patients. Perioperative recorded music is an attractive intervention specifically in this patient group, as it is safe, well-liked and reduces sedative and opioid medication requirement[26]. The study population of patients undergoing proximal femur fracture surgery was chosen because of the prevalent occurrence of postoperative delirium and high levels of postoperative pain and stress. Results of this trial will give insight in reduction of delirium in a prevalent and vulnerable patient group, as well as clarify the relation between neurohormonal stress response to surgery activity, the occurrence of delirium and postoperative complication rate.

TRIAL STATUS

The current protocol is version 3.0, dated August 15, 2018. The first patient was included on March 5, 2019 and inclusion is expected to continue until December 2021. The study is open for patient inclusion.

Authors' contributions

VXF, EMMVL, MJP, JJ and MHJV developed the study concept and design, with critical evaluation by DVDV, LJPS, RH, and JH. All authors have read, critically revised and approved the final manuscript.

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Competing interests

None.

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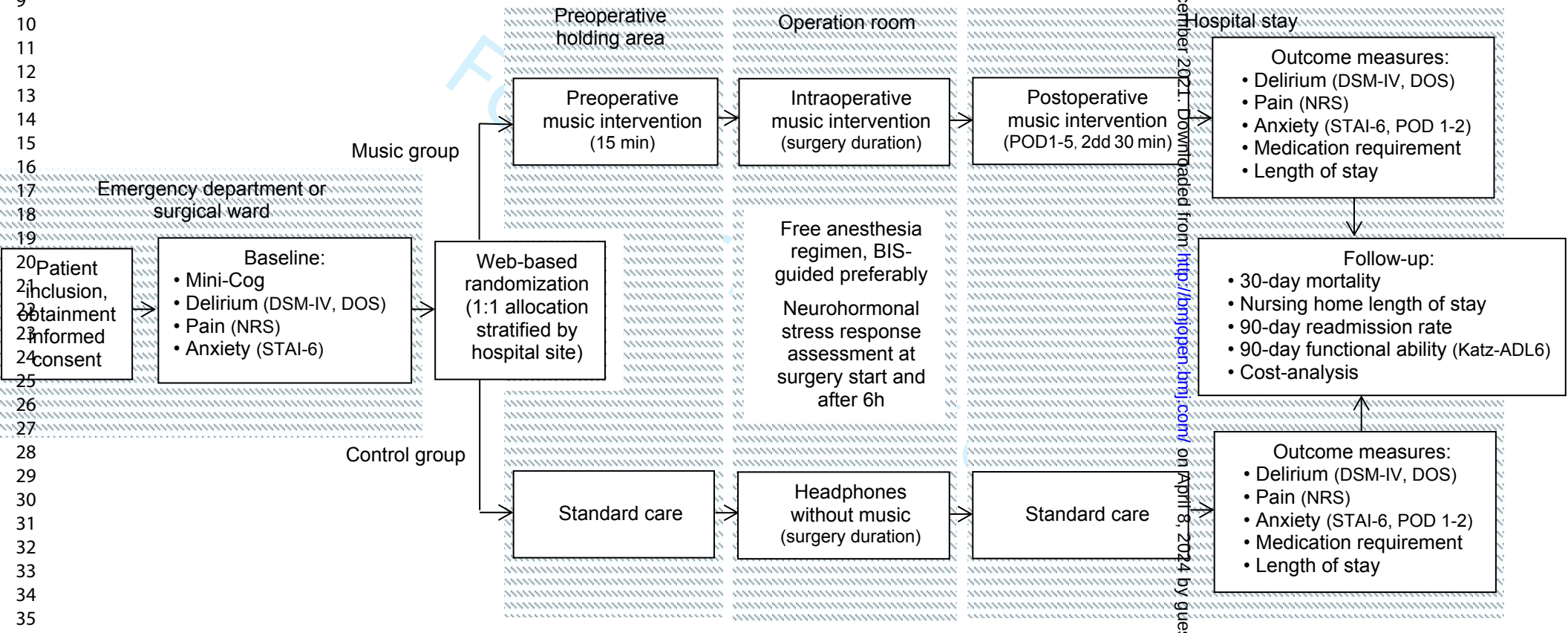
Figure 1.

MCHOPIN study overview detailing study procedures. The music intervention consists of approximately 30 hours of preselected music divided in four playlists (classical, jazz and blues, pop and Dutch music), allowing patients to choose from these lists.



SPIRIT
STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	3, 18
	2b	All items from the World Health Organization Trial Registration Data Set	18
Protocol version	3	Date and version identifier	18
Funding	4	Sources and types of financial, material, and other support	21, 22
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	21
	5b	Name and contact information for the trial sponsor	N/A
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	21
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	N/A

Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	5, 6
	6b	Explanation for choice of comparators	12, 13
Objectives	7	Specific objectives or hypotheses	6
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	7
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	7
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	8
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	12–14
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	15, 16
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	N/A
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	N/A
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	8–12
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	Figure 1

Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	14, 15
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	15
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	7
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	7
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	17
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	N/A
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	8–12
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	16, 17

Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	15
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	16, 17
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	16, 17
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	16, 17
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	15, 16
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	N/A
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	15, 16
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	N/A
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	18
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	18

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	7
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	N/A
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	15, 16
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	21, 22
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	21, 22
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	15, 16
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	18
	31b	Authorship eligibility guidelines and any intended use of professional writers	18
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	N/A
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Available on request
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	N/A

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

BMJ Open

The effect of Music on Clinical outcome after Hip fracture OPeratIoNs (MCHOPIN): study protocol of a multicentre randomised controlled trial

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The effect of Music on Clinical outcome after Hip fracture OPeratIoNs (MCHOPIN): study protocol of a multicentre randomised controlled trial

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Disclosures

None

Strengths and limitations of this study

- This multicentre randomised controlled trial investigating the effects of perioperative recorded music on delirium and postoperative recovery in 508 elderly proximal femur fracture patients will be conducted in several hospitals in the Netherlands.
- The perioperative music intervention is non-invasive and not associated with any risks or adverse events.
- Due to the profound effects of delirium on patient outcome and recovery, delirium prevention is a quality indicator in health care for many hospitals worldwide, making this a clinically relevant trial for a vulnerable patient group with study outcome measures already part of standard patient care, limiting burdening the participating patients.
- Limitations due to lack of blinding related to the music intervention can be justified, as surgical studies and studies evaluating delirium with non-pharmacological interventions can often not be blinded in general.

ABSTRACT

Background: Patients undergoing proximal femur fracture surgery are at high risk for postoperative complications, with postoperative delirium occurring in 25-40% of patients. Delirium has profound effects on patient outcome and recovery, the patient's family, caregivers, and medical costs. Perioperative music has a beneficial effect on eliciting, modifiable risk factors of delirium. Therefore, the aim of this trial is to evaluate the effect of perioperative recorded music on postoperative delirium in proximal femur fracture patients undergoing surgery.

Methods and analysis: The MCHOPIN study is an investigator-initiated, multicentre, randomised controlled, open-label, clinical trial. Five hundred and eight proximal femur fracture patients meeting eligibility criteria will be randomised to the music intervention or control group with concealed allocation in a 1:1 ratio, stratified by hospital site. The perioperative music intervention consists of preselected lists totalling 30 hours of music, allowing participants to choose their preferred music from these lists (classical, jazz and blues, pop, Dutch). The primary outcome measure is postoperative delirium rate. Secondary outcome measures include pain, anxiety, medication requirement, postoperative complications, hospital length of stay, and 30-day mortality. A 90-day follow-up will be performed in order to assess nursing home length of stay, readmission rate and functional ability to perform daily living activities. Furthermore, the cost and cost-effectiveness of the music intervention will be assessed. Data will be analysed according to an intention-to-treat principle.

Ethics and dissemination: The study protocol has been approved by the Medical Research Ethics Committee Erasmus MC on October 8, 2018 (MEC-2018-110; NL64721.078.18). The trial will be carried out following the Declaration of Helsinki principles, Good Clinical Practice guidelines and Dutch Medical Research Involving Human Subjects Act. Research data will be reported following CONSORT guidelines and study results will be published in a peer-reviewed journal.

Registration details: Dutch Trial Register (NTR7036).

Abbreviations

ASA, American Society of Anesthesiologists; AVG, Dutch Personal Data Protection Regulation (in Dutch: Algemene Verordening Gegevensbescherming); DOS, Delirium Observation Screening; DSM-IV criteria, Diagnostic Statistical Manual-IV criteria; ERAS, Enhanced Recovery After Surgery; IGZ, Dutch Health Care Inspectorate (in Dutch: Inspectie voor de Gezondheidszorg); Katz-ADL6, Katz Index of Activities of Daily Living; ME, Morphine Equivalent (1 mg ME = 1 mg of parenteral morphine; mg milligram; MMSE, Mini-Mental State Examination; NRS, Numeric Rating Scale; STAI, State Trait Anxiety Inventory; STAI-6, State Trait Anxiety Inventory-6; WMO, Medical Research Involving Human Subjects Act (in Dutch: Wet Medisch wetenschappelijk Onderzoek met Mensen).

INTRODUCTION

Proximal femur fractures are common in the elderly and are primarily treated surgically.[1] These frail patients are at a high risk for the occurrence of postoperative complications, as they often have significant comorbidity with polypharmacy use.[2] A prevalent in-hospital complication of the elderly is delirium, an acute, fluctuating, cognitive and consciousness disorder.[3] Postoperative delirium rates in elderly Dutch proximal femur fracture surgery patients have been observed to vary between 25 to 40%.[4 5] It has been associated with an increased rate of additional postoperative complications,[6] a prolonged length of hospital stay,[6 7] and higher medical costs[7]. Moreover, it has a thorough impact on the patient's family,[8 9] increasing the risk of poor long-term functional recovery and mortality rate.[10-12]

As the consequences of experiencing an episode of delirium are profound, delirium is nowadays regarded as a state of acute brain dysfunction.[13] Therefore, there is an increasing interest in delirium prevention and reduction. The exact pathophysiological mechanism of delirium is multifactorial and complex. Primary prevention with non-pharmacological interventions is generally regarded as the most accepted and effective treatment strategy,[3 14] especially since conflicting reports on the effectiveness of prophylactic drug use to prevent delirium have been reported.[15-17] Multiple modifiable precipitating risk factors have been identified.[3 18] These include increased postoperative pain levels,[19-21] higher opioid, sedative and benzodiazepine medication dosages,[21-23] as well as a more vigorous physiological stress response to surgery and elevated stress hormone cortisol level.[3 24] Current patient care aims to reduce these risk factors in order to prevent delirium.

Perioperative recorded music as a non-pharmacological intervention can reduce postoperative pain,[25] intraoperative sedative and postoperative opioid medication requirement,[26] and attenuate the physiological stress response to surgery.[26] Comparisons have been drawn with the most well-known non-pharmacological interventions for surgery, collectively known as

the Enhanced Recovery After Surgery (ERAS) protocols, which have the same objectives.[27] Moreover, the music intervention seems to be well-liked by patients, with high patient satisfaction levels and willingness to listen to perioperative music again if they were to undergo surgery in the future.[26] The effects of perioperative music on postoperative complications, patient outcome, and recovery have only sparingly been investigated,[26 28] with most studies focusing on postoperative pain levels, anxiety or medication requirement in the first few days after surgery. To date, only four small studies in elective knee and hip replacement surgery with sample sizes of 60 patients or less examined the effect of music on confusion and cognitive functioning in adult surgical patients.[29-31] Only two used a delirium screening tool,[32 33] but positive results were reported in all studies.

This multicentre randomised controlled trial will investigate whether perioperative music can reduce the occurrence of postoperative delirium in elderly proximal femur fracture patients undergoing surgery. Secondary objectives are to assess the effects of perioperative music on pain, anxiety, medication use, postoperative complications, neurohormonal stress response, hospital length of stay, nursing home length of stay, 30-day mortality, 90-day readmission, 90-day functional ability to perform daily living activities, costs, and cost-effectiveness.

METHODS AND ANALYSIS

Trial design and setting

The MCHOPIN study is an investigator-initiated, multicentre, randomised controlled, open-label, clinical trial. Proximal femur fracture patients meeting eligibility criteria will be randomised to the music intervention or control group using a secure web-based, computerized randomisation system with concealed allocation in a 1:1 ratio, stratified by hospital site. Only study staff members and their delegates will have login credentials. The randomisation code for allocation will be kept concealed from the study staff recruiting patients. The music group will receive recorded music as an intervention before, during and after surgery, whilst the control group will not but will wear headphones without music during surgery instead. The study will take place in three non-academic hospitals and one academic hospital. Patients will be followed until 90 days after the proximal femur fracture surgical procedure.

Eligibility, recruitment and consent

Potential eligible patients will be informed about the MCHOPIN study while in the emergency department or upon admission to the surgical ward. Information will be provided verbally as well as on paper through a patient information folder with an informed consent form (Supplementary file 1). Patients meeting eligibility criteria and willing to participate will be randomised after written informed consent obtainment. In general, proximal femur fracture patients will be operated within 48 hours of hospital admission based on guidelines set by the Dutch Health Care Inspectorate (in Dutch: Inspectie voor de Gezondheidszorg (IGZ)). Therefore, it is not possible to give patients more than a day to consider participation. However, the intervention is non-invasive and not associated with any risks or adverse events[26]. As beneficial effects of music on disruptive behaviour and cognition in dementia patients have been reported[34], proximal femur fracture surgery patients with dementia are not excluded from study

participation, although written informed consent by the proxy is necessary (Supplementary file 2). The information folders for patient and proxy and informed consent forms follow the standard template outlined by the Central Committee on Research Involving Human Subjects (CCMO), the competent authority for research in the Netherlands, and the Dutch Clinical Research Foundation. Patients with hearing aids can also readily participate, which has been consulted with the Erasmus MC auditory centre.

Inclusion criteria:

1. Patients with a proximal femur fracture undergoing surgical treatment
2. Age ≥ 65 years old
3. Provision of written informed consent by patient or proxy

Exclusion criteria

1. Additional serious injuries or additional surgical procedures that may affect any of the outcome parameters
2. Simultaneous bilateral hip fracture
3. Implant in situ in the affected hip
4. Severe hearing impairment, defined as no verbal communication possible
5. Patients unwilling or unable to comply with the intervention
6. Preoperative planned hospital discharge and return to nursing home within 48 hours of admission
7. Insufficient knowledge of the Dutch or English language to understand the study documents in the judgement of the attending physician or researcher
8. Participation in another intervention study that might influence the duration of surgery or any of the outcome parameters

Primary outcome

The primary outcome measure is postoperative delirium. Participating patients will be screened using the Delirium Observation Screening (DOS) scale, a diagnostic nursing screening tool. The DOS scale is a 13-item scale facilitated in order to recognize delirium early, with valid consistency and reliability in both geriatric patients and elderly hip fracture patients.[35 36]
The DOS end score is the sum of the three DOS scales, assessed during each shift by the nurse, divided by 3. A DOS end score ranges between 0 and 13. In a study of 92 hip fracture patients, a DOS end score of 3 or more had a 94.4% sensitivity of delirium, while a score less than 3 had a 76.6% specificity.[35 36] Because the DOS scale is easy in use, requires no active patient participation and has been validated in several trials,[37 38] it is a standard part of multidisciplinary delirium prevention measures in proximal femur fracture patients in the Dutch National Guidelines on delirium. In case of a DOS end score of 3 or more, the geriatrician will be consulted for patient assessment to confirm clinical diagnosis of delirium using the Diagnostic Statistical Manual-IV (DSM-IV) criteria. These criteria define delirium as an acute, fluctuating disturbance of consciousness with inability to focus and shift of attention, caused by a general medical condition. In all participating hospitals, a geriatrician is part of and actively involved in the proximal femur fracture surgery patient care team.

Secondary outcomes

Secondary outcome measures are:

- Postoperative pain, assessed using an 11-point numeric rating scale (NRS), in which 0 implies no pain and 10 implies the worst pain possible.
- Anxiety, assessed using the State-Trait Anxiety Inventory-6 (STAI-6).[39] Feelings of anxiety are reported on a four-point Likert scale for each item, with a score between 20 and 80 points for each questionnaire. Scoring is achieved by reverse scoring the 3 positive items, sum all 6 scores, and multiply the total score by 20/6. A higher score

correlates to a higher level of anxiety. The State-Trait Anxiety Inventory (STAI), consisting of two 20-item subscale questionnaires, is one of the most frequently used anxiety questionnaires in clinical research.[40] The state subscale measures situation related anxiety, anxiety at the very moment, while the trait subscale measures disposition related anxiety, anxiety as a general personal characteristic trait). A major drawback of the STAI is its length, especially in a study population of elderly patients with frequent cognitive impairment, pain and opioid requirement. In order to increase compliance and minimize unanswered items, the 6-item short form of the STAI-state by Marteau and Bekker (1992) will be used.[39] The STAI-6 has a high internal reliability and correlation with the full-form STAI,[39 41 42] has been used in clinical research in elderly patients,[43 44] and has been validated in Dutch.[45]

- Medication use, consisting of intraoperative and postoperative opioid medication, as well as postoperative benzodiazepines and postoperative antipsychotic medication for the treatment of delirium. Data will be collected from the electronic patient file. Analgesic opioid medication will be converted to milligrams of morphine equivalents (1 mg ME = 1 mg parenteral morphine).
- Postoperative complication rate. Data will be collected from the electronic patient database and classified according to the Clavien-Dindo classification.[46]
- Neurohormonal stress response, assessed by measuring serum cortisol. An increased stress response after surgery has been associated with an increased risk of postoperative delirium.[24] The duration until peak cortisol level depends on the surgical severity and is an indicator of intrinsic physiological stress.[47] Peak levels of cortisol are observed 4 hours after start of surgery in moderate and after 8 hours in major surgical procedures. Proximal femur fracture surgery is generally classified as a major surgical procedure. Therefore, the second serum cortisol will be drawn 6 hours after the first

sample. This will be combined with the blood draw postoperatively for the postoperative serum haemoglobin measurement, which is part of standard surgical care.

- Hospital length of stay in days, as calculated from the hospital admission date until declared 'medically ready for discharge' by the attending physician as recorded in the patient's medical file. Also the full length of stay until the actual discharge from hospital will be assessed.
- 30-day mortality, as calculated from date of admission.
- Nursing home length of stay in days, as calculated from nursing home admission date until discharge.
- 90-day readmission, as calculated from date of admission.
- 90-day functional ability to perform daily living activities, which will be assessed during standard postoperative outpatient visit 3 months postoperatively using the Katz Index of Activities of Daily Living (Katz-ADL6). This 6-item instrument assesses basic activities of daily living in 6 functions, with a total score of 6 indicating full function and a score of 2 or less severe functional impairment.[48]
- Through an economic evaluation, the cost-effectiveness of the music intervention will be investigated, using the method of cost-effectiveness analysis (CEA). The evaluation will be conducted from a healthcare perspective, with a time horizon of 90 days. It will make a comparison between the intervention and the control group by identifying, measuring, and valuing the costs and patient outcomes of both treatment strategies. The costs will include costs of the initial hospital admission (either on the ward or on the intensive care unit), primary surgery and additional procedures (including surgical re-interventions), medications, diagnostic imaging, in-hospital consultations, and costs for headphones and sound equipment. The analysis will take into account costs after hospital discharge, including costs of outpatient consultations, visits to the emergency room, consultations with the general practitioner, home care, and nursing home admissions. Data on

resource consumption will be collected from the electronic patient database and using a custom follow-up questionnaire. These data will then be combined with unit costs to generate patient-level costs. Costs of productivity losses will be ignored in this study, because these are expected to be minor, given the age range of the patients. Regarding patient outcomes, the CEA will consider the occurrence of delirium (as defined above). An incremental cost-effectiveness ratio (ICER) will be calculated as the difference in cost between the two treatment strategies divided by the difference in effectiveness, unless one treatment dominates the other (i.e., has lower costs and greater effects). This ICER will be expressed as incremental costs per case of delirium prevented.

Additional study parameters assessed will be patient demographic characteristics, preoperative medication use, medical and surgical patient history, living situation prior to hospital admission, education level, injury and treatment characteristics, and music preferences and its importance in daily life. Cognitive functioning, a prominent risk factor for delirium,[49] will be screened preoperatively using the Mini-Cog, a three-item screening questionnaire with high correlation to cognitive functioning assessment by the Mini-Mental State Examination (MMSE).[50 51]

Study intervention

The music group will listen to music preoperatively, intraoperatively and postoperatively during the first five days after surgery. The preoperative music intervention will be ideally at least 15 minutes, as a relatively short exposure time seems to already have an effect.[26] The intraoperative music intervention will start after anaesthesia induction until the patient choses to remove the headphone in the recovery room. Postoperatively, the music group will listen to music twice a day for 30 minutes, starting from the first until the fifth postoperative day or until patient discharge. Previous studies have reported noise levels exceeding 100 decibels adjusted during surgery.[52] As noise pollution during surgery is possibly associated with a negative effect

on patient outcome,[53] with higher noise levels reportedly increasing postoperative complications rate and stress hormone levels.[54-56] Therefore, the control group will receive standard patient care and in addition wear headphones intraoperatively without music in order to avoid possible criticism that the observed effects are solely due to noise reduction and not through music. Before and after surgery, noise levels are generally quite lower compared to during surgery.[53] A recent study reported that awake patients might have increased anxiety due to wearing headphones,[57] which is also the reason why noise-cancelling headphones blocking all ambient noise are not used.

The music intervention consists of preselected music divided in four playlists (classical, jazz and blues, pop, and Dutch music) providing approximately 30 hours of music using a tablet. Patients are allowed to choose music from these list, as the largest beneficial effects were previously observed when patients selected music from a preselected playlist.[25] Moreover, it is unlikely that patients with a proximal femur fracture admitted through the emergency department after transport by ambulance will bring their own favourite music. Music was selected by a panel of five research physicians with extensive knowledge of perioperative music, based on literature recommendations and music used in previous studies. Care was taken to choose popular music from the patients' youth and early adulthood (50's to 80's) which would likely be familiar to the patient, as a familiar environment can reduce the occurrence of delirium[58]. Consent was obtained from the music copyright managing organizations in the Netherlands, Buma Association and Stemra Foundation (Dutch: Vereniging Buma and Stichting Stemra), to use recorded music for study research purposes.

The Lenovo Tab E7 16 GB and disposable HP 112 Fetum, medically approved headphones will be used as music devices, along with the free AIMP audio player which are easy to use and require minimal effort to select the preferred music list. The tablet also allows for magnification in order to assist visually impaired participants to choose the music.

Study procedures

A timeline detailing study procedures and outcome measures is presented in Figure 1. After signing informed consent and computerized randomisation, the Mini-Cog will be administered and baseline NRS for pain and STAI-6 will be filled out also by all participants, followed by preoperative geriatric consult and DOS scores as part of standard care. A custom-made demographic questionnaire on preoperative living situation, education level and music will be provided as well.

The preoperative music intervention for the music group will start from the surgical ward when the patient is called up for surgery and continue until arrival in the operating room, whereas the control group will receive standard care preoperatively. The anaesthesiologist and surgical team will be free to decide whether general or locoregional anaesthesia will be used, as well as the anaesthesia regimen, reflecting daily clinical practice. Beneficial effects of music on postoperative pain and opioid requirement have been observed during both general and locoregional anaesthesia,[26] even when music is solely played intraoperatively when compared to headphones without music.[59] Preferably, anaesthesia administration will be guided by using a bispectral index monitor or comparable anaesthesia depth monitoring device. Whilst a recent meta-analysis reported that significantly less propofol is needed to reach the same sedation level measured using bispectral index when listening to music intraoperatively, the majority of hospitals employ volatile anaesthesia for sedation regarding proximal femur fracture surgery. Therefore, the intraoperative sedative dosages are not recorded. After induction, the first cortisol blood sample will be drawn and all subjects will receive headphones. The control group will wear headphones in order to assess the music intervention and not noise reduction. All participants will wear headphones until arrival in the recovery room, where they can chose to remove them when they wish. No corticosteroids will be administered between the first and second cortisol blood sample drawing (6 hours after the first blood sample), unless this is

deemed clinically necessary by the patient care team. As previously mentioned, cortisol will not be assessed in a selected group of patients participating in his trial.

For all participating patients postoperatively, the DOS will be assessed thrice daily, with the geriatrician actively involved in proximal femur fracture surgery patient care. The NRS for pain will be assessed daily and postoperative opioid dosage will be administered based on the NRS and care team observations. The STAI-6 will be filled out by all participants during the first and second postoperative day. Data on the NRS for pain, DOS, postoperative medication requirement, postoperative complication rate, hospital length of stay and 30-day mortality rate will be retrieved from the electronic patient database. All participants will be followed until three months postoperatively. Two questionnaires, the custom-made follow-up questionnaire and the Katz-ADL6 questionnaire, will be administered during either the outpatient follow-up visit or by phone. The follow-up questionnaire will assess nursing home length of stay, 90-day readmission rate, and information needed for the economic evaluation.

Sample size calculation

Literature on the frequency of postoperative delirium in proximal femur fracture surgery patients varies between 15 and 60 percent,[2] with a recent meta-analysis reporting an accumulated prevalence of 24 percent.[60] Delirium in Dutch proximal femur fracture surgery patients over 65 years of age has been observed in 19 to 37 percent of patients.[61 62] Previously, a meta-analysis assessing effectiveness of different, mostly non-pharmacological interventions reported a reduction in delirium rates of 13%.[63] In order to assess a minimally clinical relevant reduction of 13% in delirium frequency when taking 15-60% of delirium into account, with a power of 80%, alpha of 5% and planned two-sided testing, taking into account possible in-hospital mortality and loss-to-follow-up of 10% overall, 508 patients should be enrolled (254 per group).

Data collection and management

Clinical research assistants will be available at participating hospital sites to assist in executing study procedures and data collection. Research data will be collected using questionnaires and with a case report forms with data from the electronic patient database. The handling of personal data will comply with the Dutch Personal Data Protection Regulation (in Dutch: Algemene Verordening Gegevensbescherming, AVG). Research data will be stored electronically in a database with an audit trail that meets Good Clinical Practice standards (OpenClinica) and will be handled confidentially. Any information on paper collected during this study will be placed in a research folder, which will be filed in locked cabinets in research offices at the participating hospitals. Data will be stored during the study period and for a period of 15 years after completion of the study.

Monitoring, safety and auditing

An appointed monitor will develop standard procedures and details on the monitoring activities. The sponsor/investigator has a liability insurance which is in accordance with the Medical Research Involving Human Subjects Act (in Dutch: Wet Medisch wetenschappelijk Onderzoek met Mensen, WMO). The Medical Research Ethics Committee Erasmus MC has given dispensation from the statutory obligation to provide insurance for subjects participating in medical research, as participation in this study is considered to be without risks.

No deleterious or negative adverse side-effects associated with listening to music as a perioperative intervention are known[26]. In accordance, the investigator will report all serious adverse events to the sponsor, except for the specific serious adverse events which are considered not related to the music intervention and common in proximal femur fracture surgery patients. A maximum sound level will be ensured to prevent hearing damage. The headphones and sound equipment will be cleaned with a damp microfiber cloth and the ear pads or buds replaced after use by a patient during hospital stay, in order to reuse the devices, in accordance with the Erasmus MC Infection Prevention Unit and local hospital protocols. No additional or

enhanced hygiene measures will be needed concerning the use of headphones and sound equipment in the operating room complex and the same sound equipment set will be used on the ward.

Statistical analysis

Data will be analysed using the Statistical Package for the Social Sciences (SPSS) version 24.0 or higher (SPSS, Chicago, Ill., USA). Normality of continuous data will be tested with the Shapiro-Wilk test. Homogeneity of variances will be tested using the Levene's test. A two-sided p-value <0.05 will be taken as threshold of statistical significance in all statistical tests. The analyses will be performed on an intention to treat basis. Should there be 5% crossovers, a per protocol analysis will also be done. If necessary, missing values will be replaced using multiple imputations following the predictive mean matching method, using ten imputations.

Descriptive analysis will be performed in order to report the outcome measures for both treatment groups. For continuous data, the mean and SD (parametric data) or the median and percentiles (non-parametric data) will be reported per treatment group. For categorical data, numbers and frequencies will be reported per treatment group. The only exception is that costs will be reported as mean with 95% confidence interval (95% CI). The 95% CI around the mean costs will be approximated by nonparametric bootstrapping. Continuous data will be tested using the Student's T-test or the Mann-Whitney U-test, as appropriate. Categorical data will be tested using the Chi-squared or Fisher's Exact test, as applicable. Both univariable and multivariable analysis will be performed. A binary logistic regression model (for binary outcomes) or multivariable linear regression model (for continuous outcomes) will be developed, with the outcome as dependent variable and the study group (i.e., intervention or control) as covariate. Patient, injury, and treatment variables that differ between the groups and may confound the association of the intervention and outcome will be entered into the model. Variables will be entered into the model if univariate analysis produces a p-value of 0.05 or

lower. The unadjusted and adjusted odds ratio's (for binary outcomes) and beta values (for continuous outcomes) will be reported with 95% confidence interval. A subanalysis for all outcome measures will be performed by stratifying patients according to their age (<80 and ≥ 80 years).

Blinding

Patients enrolled in the MCHOPIN study will not be blinded to the music intervention. While the surgical team will be blinded intraoperatively on paper as all patients will wear headphones during surgery, in practice it will not be possible to blind the surgical team as patients can adjust the music volume or ask for a different playlist whilst in the operating room or postoperatively on the surgical ward. The clinical chemist and laboratory site concerned with the analysis of the neurohormonal cortisol stress response samples will be blinded to the intervention. Also, a part of the statistical analysis, which includes the primary and almost all of the secondary outcome measures except the economic analysis, will be performed by a statistician blinded to the music intervention.

Patient and Public Involvement

No patients and public were involved in the study design, recruitment to and conduct of the study, nor in assessing the burden of the intervention.

ETHICS AND DISSEMINATION

This study will be conducted in accordance to the principles of the Declaration of Helsinki (64th WMA General Assembly, Fortaleza, Brazil, 2013) and in accordance to the Medical Research Involving Human Subjects Act (in Dutch: WMO). Written informed consent will be obtained from each patient or proxy.

Ethics approval and trial registration

Approval by the Medical Research Ethics Committee Erasmus MC was obtained on October 8, 2018 (MEC-2018-110; NL64721.078.18). Local approval in the participating hospitals followed suite and the study was open for inclusion starting from March 5, 2019. The trial protocol has had no substantial amendments to the original protocol. This trial has been registered in the Dutch Trial Register (NTR7036).

Dissemination policy

Research data will be reported following the Consolidated Standards of Reporting Trials (CONSORT) guidelines[64]. No research data that can be traced to individual persons will be presented or published. On completion of the trial, the research team aims to publish the manuscript in a peer-reviewed journal and present results in national and international conferences. Each participating hospital will be invited to provide co-authors for a collaborator group authorship, consisting of one trauma surgeon and one anaesthesiologist, provided that 15 percent of the total required study sample size is included at that site. All participating hospitals will be acknowledged for their participation.

DISCUSSION

Delirium is a prevalent complication in in-hospital elderly patients and is associated with prolonged hospitalisation due to an increased risk of postoperative complications and mortality. It also leads to long-term cognitive and functional impairment[3 6 7 10 11]. Therefore, an increasing research interest in delirium prevention and treatment has developed over the past two decades. Delirium prevention is currently a health care quality indicator in many countries worldwide[65]. Several non-pharmacological multimodal intervention programs have reported beneficial results on reducing delirium[3 16], especially since the pharmacological prevention and treatment of delirium remains somewhat controversial[3 16 17 66]. Given the multifactorial factors involved in delirium development, current guidelines consist of both multimodal pharmacological and non-pharmacological interventions. While no clinical useful biomarker for delirium has currently been identified yet[67], serum cortisol reportedly has delirious effects when increased[68-71]. It has been theorized that overstimulation of the hippocampus, rich in glucocorticoid receptors and therefore susceptible for cortisol and stress, plays a role in delirium development[72]. Given that perioperative music can attenuate the neurohormonal cortisol stress response[26], combined with the significant beneficial effects of perioperative music on postoperative pain, anxiety, intraoperative sedative requirement and postoperative opioid usage[25 26], the multicentre, randomised controlled, clinical MCHOPIN trial will assess the effect of perioperative recorded music on postoperative delirium, patient outcome and recovery in elderly proximal femur fracture surgery patients.

An exhaustive literature search with a biomedical information specialist was performed on October 16th, 2020 in order to assess current literature on perioperative music and postoperative delirium in adult surgical patients. Only four randomised controlled trials evaluated the effect of music on postoperative cognitive functioning and delirium. McCaffrey and Locsin *et al.* reported significant lower acute confusion episodes in two trials with 190 elderly patients

undergoing elective hip or knee surgery[30 31]. However, confusion was ascertained by reading the nurse's narrative notes without use of screening tools for delirium recognition. Two other studies observed significantly lower rates of postoperative acute confusion ascertained using the validated NEECHAM Acute Confusion Scale when patients listened to music postoperatively compared to standard care. Sample sizes were relatively small, with only 22 and 60 elective hip and knee surgery patients included[32 33].

In the MCHOPIN study, the DOS score will be used to pro-actively screen for delirium in all participants during each nursing shift[35 37]. Given that delirium is often not recognized or misdiagnosed, a strong point of this trial is that all participating hospitals are high volume centres which actively involve the geriatrician in the care of all admitted proximal femur fracture surgery patients. Both patients and practitioners will not be blinded, as the beneficial effects of perioperative music seem largest when music is applied before, during and after surgery instead of only intraoperatively during general anaesthesia[25 26]. Also, a significant portion of proximal femur fracture surgery patients is operated on while receiving locoregional anaesthesia.
We believe it acceptable that no blinding is applied, as patients cannot be blinded in many surgical trials. Only 3 and 37% of practitioners and patients were blinded in high impact surgical randomised controlled trials[73]. Moreover, primary prevention of delirium is generally accepted to be most effective with non-pharmacological interventions[3], meaning blinding is not possible. The anaesthesiologist and surgical team will be free to decide the manner of anaesthesia and perioperative analgesia regimen. Given the number of patients that will be enrolled in this trial and the stratification per hospital site, it is assumed that this will balance itself out and no differences in locoregional or general anaesthesia and analgesia medication will be observed between the intervention and the control group.

To our knowledge, this is the first large, multicentre, randomised controlled trial investigating the effect of perioperative recorded music on postoperative clinical patient outcome and recovery which also employs a reasonable follow-up time after patient discharge.

Moreover, only a limited number of studies evaluating perioperative music involved acute care or elderly surgical patients. Perioperative recorded music is an attractive intervention specifically in this patient group, as it is safe, well-liked and reduces sedative and opioid medication requirement[26]. The study population of patients undergoing proximal femur fracture surgery was chosen because of the prevalent occurrence of postoperative delirium and high levels of postoperative pain and stress. Results of this trial will give insight in reduction of delirium in a prevalent and vulnerable patient group, as well as clarify the relation between neurohormonal stress response to surgery activity, the occurrence of delirium and postoperative complication rate.

TRIAL STATUS

The current protocol is version 3.0, dated August 15, 2018. The first patient was included on March 5, 2019 and inclusion was originally expected to continue until December 2021 at time of inception, but is now projected to continue until 2022. The study is open for patient inclusion.

Authors' contributions

VXF, EMMVL, MJP, JJ and MHJV developed the study concept and design, with critical evaluation by DVDV, LJPS, RH, and JH. All authors have read, critically revised and approved the final manuscript.

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Competing interests

None.

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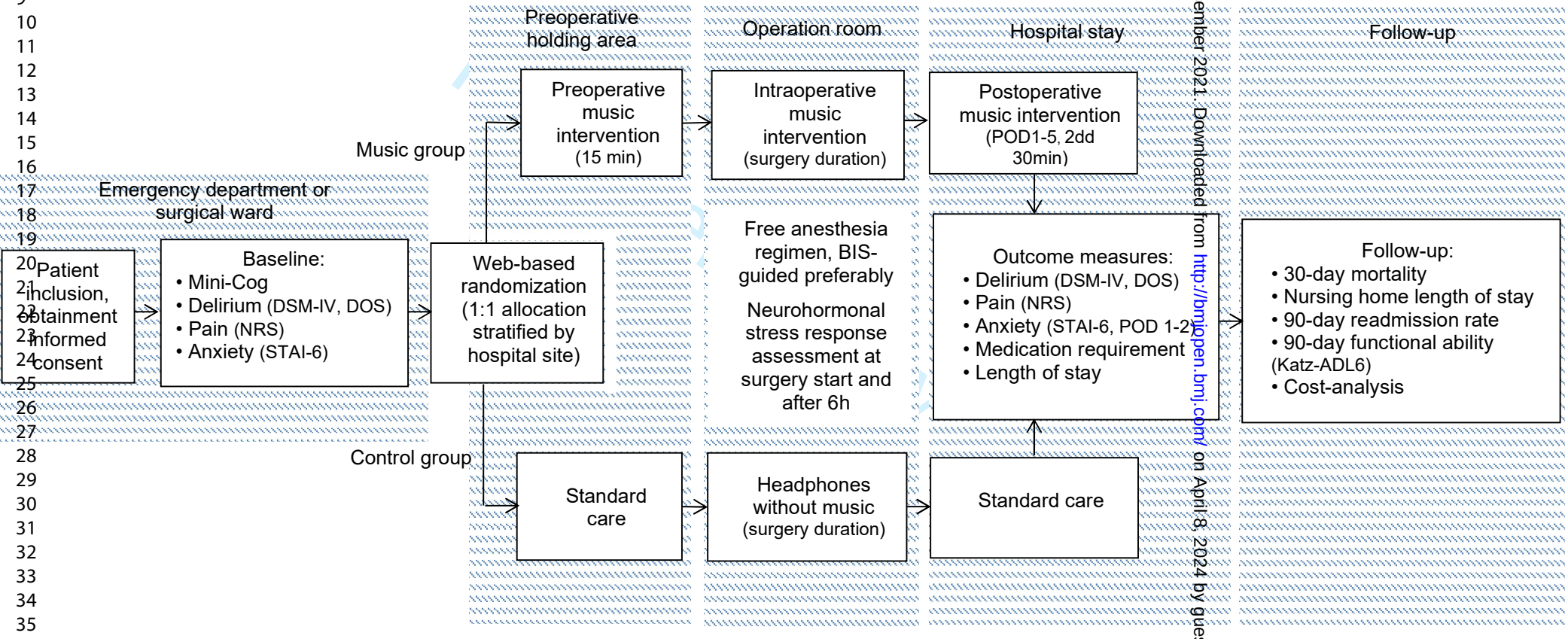
Figure 1.

MCHOPIN study overview detailing study procedures. The music intervention consists of approximately 30 hours of preselected music divided in four playlists (classical, jazz and blues, pop and Dutch music), allowing patients to choose from these lists.



Erasmus MC
Universitair Medisch Centrum Rotterdam

Subject information for participation in medical scientific research

Effect of music on the clinical outcome after hip fracture operations (MCHOPIN): a multicenter randomized controlled trial

Introduction

Dear Sir/Madam,

You are asked to take part in a medical-scientific study (the MCHOPIN study). Participation is voluntary. Participation requires your written consent. You have received this letter because you have broken your hip and will undergo surgery. Before you decide whether you want to participate in this study, you will be given an explanation about what the study involves. Please read this information carefully and ask the investigator for an explanation if you have any questions. You can also ask the independent expert, who is mentioned at the end of this document, for additional information. You may also discuss it with your partner, friends or family. Additional information about participating in a study can be found in the enclosed general brochure on medical research.

1. General information

This study has been set up by the Erasmus MC and will be conducted by trauma surgeons in various hospitals in the Netherlands. For this study, 508 study subjects are required. The Medical Research Ethics Committee (MREC) Erasmus MC has approved this study. General information about the assessment of research can be found in the general brochure on medical research.

2. Purpose of the study

Scientific research has shown that music during and around surgery can have a beneficial effect on pain and anxiety. The purpose of this study is to assess the effect of music during and around surgery for a broken hip. Among other

things, the effect of music on delirium, pain, anxiety, medication requirement, complications after surgery, stress response of the body, length of hospital stay and / or length of nursing home stay and daily functional ability after surgery will be investigated.

3. Background of the study

It is known that 25-40% of patients with a broken hip in the Netherlands develop delirium, a sudden episode of confusion and disturbance of consciousness. This can lead to other complications after surgery, a prolonged hospitalization and a negative effect on recovery. Therefore, measures are taken to prevent delirium. For example, this is done by treating or reducing risk factors, like pain and stress. Because of the beneficial effect of music on pain and stress, we would like to assess whether music can reduce the occurrence of delirium. The benefit of music compared to other ways of treatment is that it is easy and durable, without side effects.

4. What participation involves

Your participation will last until 3 months after your surgery.

Treatment

In this study, half of the subjects will listen to music before, during and after surgery during hospital stay. The other half of the subjects will not listen to music. The music consists of a preselected music list by the investigators, and subjects of the music group will be allowed to choose from this list. It will be determined by drawing lots whether or not you will listen to music. Additional information about this can be found in the enclosed general brochure on medical research.

If you have drawn the music group, you will receive a headphone and listen to music before surgery during 15 minutes. If you are using a hearing aid, you will be asked to take it off and to adjust the music volume to a pleasant level. During surgery, you will listen to music until leaving the recovery room. After surgery, you will listen to music twice a day for 30 minutes during the first 5 days of your hospital stay after surgery. If you have not drawn the music group, you will wear a headphone without music 15 minutes before surgery

until leaving the recovery room. You are not allowed to listen to music during the first 5 days of your hospital stay after surgery, if you have not drawn the music group.

Visits and measurements

An additional time investment from your part is required. During your hospital stay, you will be asked:

- to fill in a pain score once a day, which takes less than 1 minute to complete.
- to fill in once a 6-item questionnaire on your level of education, living situation and the role of music in your life, which takes approximately 5 minutes to complete.
- to fill in a 6-item questionnaire on anxiety once before and 2 times after surgery, which takes approximately 5 minutes to complete.
- to fill in a 3-item questionnaire on cognition once before surgery. This questionnaire will be administered to you by the attending physician or investigator.
- for 2 blood samples to measure the cortisol level, a measurement for the body's stress response. The first sample will be drawn at the start of surgery. For the second blood sample, an extra tubule of blood will be drawn for this study during a routine blood collection after surgery for a broken hip.

During the regular outpatient hospital visit 3 months after surgery, you will be asked:

- to fill in once an 8-item follow-up questionnaire on whether or not you have been readmitted to hospital, which takes approximately 5 to 10 minutes to complete.
- to fill in once a 6-item questionnaire on daily functional ability, which takes approximately 5 minutes to complete.

Furthermore, the investigator and investigator assistant will collect data from the electronic patient database to answer the research question of this study. This consists of personal data, like age and data on your surgical procedure, medication use, complications and hospital stay. If necessary, one of the

investigators will contact the hospital pharmacy, to assess which medicines you received during the hospital stay. If you stay in a nursing home or care home after discharge from hospital, one of the investigators will contact it for information on the duration of your stay.

Other than standard care

If you have drawn the music group, you will listen to music during and around your surgery, both groups will fill in the afore mentioned questionnaires and pain scores and blood will be drawn twice. If you have drawn the control group, you are not allowed to listen to music during and around your surgery and the first five days after your surgery, even though you might have done this normally. The daily care during your hospital stay remains unchanged. This study will end after your regular outpatient hospital visit, 3 months after your discharge. No additional study-related visits are required. If no outpatient visit is planned at that time after your operation, one of the investigators will contact you.

5. What is expected of you

In order to carry out the study properly, it is important that you follow the study instructions.

The study instructions require that you:

- listen to music before, during and the first 5 days after surgery only at the aforementioned moments if you have drawn the music group.
- do not listen to music before surgery, during surgery and during the first 5 days after surgery if you have not drawn the music group.
- do not participate in another medical study.
- fill in the afore mentioned questionnaires and pain scores, and that twice a tubule of blood will be drawn.

It is important that you contact the investigator:

- if you are admitted or treated in an hospital
- if you no longer want to participate in the study.
- if your contact details change.

6. Possible side effects, complications and discomforts

The music intervention is safe and has no known side effects or complications. To prevent hearing loss, a maximum sound level has been set. Drawing blood can hurt and can in some cases lead to bruising.

7. Possible advantages and disadvantages

It is important that you properly weigh up the possible benefits and disadvantages before you decide to join. Your participation can contribute to more knowledge on delirium and the use of music in health care.

Music could potentially have a beneficial effect on delirium, pain and anxiety after surgery, but this is not certain. Disadvantages of participating in this study can be:

- the extra time it will require
- the instructions you need to follow
- not being able to listen to music during the first 5 days after your surgery
- filling in the questionnaires and pain scores
- drawing of blood

All these aspects have been described above under points 4, 5 and 6.

8. If you do not want to participate or you want to stop participating in the study

It is up to you to decide whether or not to participate in the study. Participation is voluntary. If you do not want to participate, you will be treated as usual for a broken hip. If you do participate in the study, you can always change your mind and decide to stop, at any time during the study. You will then be treated as usual for a broken hip. You do not have to say why you are stopping, but you do need to tell the investigator immediately. The data collected until that time will still be used for the study.

If there is any new information about the study that is important for you, the investigator will let you know. You will then be asked whether you still want to continue your participation.

9. End of the study

Your participation in the study stops when:

- you have completed the outpatient visit and the measurements as described under point 4
- you choose to stop
- the investigator considers it best for you to stop
- the sponsor (Erasmus MC), the government or Medical Research Ethics Committee, decides to stop the study.

The study is concluded once all the participants have completed the study.

10. Usage and storage of your data and bodily material

Your personal data and bodily material will be collected, used and stored for this study. This concerns data such as your name, address, date of birth and data about your health. Also, blood is required for this study. The collection, use and storage of your data and your bodily material are required to answer the questions asked in this study and to publish the results. We ask your permission for the use of your data and bodily material.

Confidentiality of your data and bodily material

To protect your privacy, your data and your bodily material will be given a code. Your name and other information that can directly identify you, will be omitted. Data can only be traced back to you with the encryption key. The investigator and investigator assistants are the only people who will know which code you have. This is necessary, as they will have to collect information from the electronic patient database, questionnaires and bodily material. The data and bodily material that is sent to the sponsor will only contain the code, not your name or other data with which you can be identified. The key to the code will stay with the investigator. The data cannot be traced back to you in reports and publications about the study.

Access to your data for verification

Some people can access all your data at the research location. Including the data without a code. This is necessary to check whether the study is being

conducted in a good and reliable manner. Persons who have access to your data for review are members of the research team, a monitor working for the sponsor of the study, and national supervisory authorities, for example, the Healthcare and Youth Inspectorate. They will keep your data confidential. We ask you to consent to this access.

Retention period of your data and bodily material

Your data must be kept for 15 years at the research location (Erasmus MC). Your bodily material will be destroyed immediately after use.

Withdrawing consent

You can withdraw your consent to the use of your personal data at any time. This applies to this study. The study data collected until the moment you withdraw your consent will still be used in the study. Your bodily material will be destroyed after your consent has been withdrawn. If measurements have already been made with that bodily material, then this data will still be used.

More information about your rights when processing data

For general information about your rights when processing your personal data, you can consult the website of the Dutch Data Protection Authority.

If you have questions about your rights, please contact the person responsible for the processing of your personal data. For this study, that is: Erasmus MC. See Appendix A for contact details and website.

If you have questions or complaints about the processing of your personal data, we advise you to first contact the research location. You can also contact the Data Protection Officer of the Erasmus MC (See Appendix A. Contact details) or the Dutch Data Protection Authority.

Registration of the study

Information about this study is included in a list of medical-scientific studies namely the Dutch trial registry (www.trialregister.nl). It does not contain any information that can be traced to you. After the study, the website may display

a summary of the results of this study. You can find this study under MCHOPIN.

11. Study subject insurance

This study is not associated with any additional risks for you. The MREC Erasmus MC has therefore decided that the sponsor does not need to take out additional insurance.

12. Informing GP and contact with the hospital pharmacy

We will always send your GP a letter to let them know that you are participating in the study. This is for your own safety. If you do not agree to this, you cannot participate in this study. You cannot participate in the study if you do not have a GP.

During this study, the effect of music on medication use will be assessed. Therefore, the investigators will contact the hospital pharmacy to ask about your medication use. You cannot participate in this study if you do not want this.

13. No Compensation for participation

Participation in this study and use of the sound equipment is free of charge for you. You will not be paid for your participation in this study.

14. Any questions?

If you have any questions, please contact the study team. If you would like any independent advice about participation in this study, you may contact the independent doctor. He knows about the study but is not involved in it. If you have any complaints, you may contact the complaint officer at your hospital. All the relevant details can be found in Appendix A: Contact details.

15. Signing the consent form

When you have had sufficient time for reflection, you will be asked to decide on participation in this study. If you give permission, we will ask you to confirm this in writing on the appended consent form. By your written permission you indicate that you have understood the information and consent to participation

in the study. The signature sheet is kept by the investigator. You will get a copy or a second copy of this consent form.

Thank you for your attention.

16. Appendices to this information

A. Contact details
B. Informed Consent Form subject
C. Medical Scientific Research Brochure. General Information for Study Subjects (version 01-03-2017)

Appendix A: contact details for Erasmus MC

Principle investigator:

Prof. dr. M.H.J. Verhofstad, trauma surgeon Tel. no.: 010-7031050

Available during office hours. You can contact the general number of the hospital (tel. no. 010-7040704) outside of office hours and ask for the attending of the (trauma)surgery department.

Coordinating investigator:

Mr. V.X. Fu, research physician Erasmus MC Tel. no.: 06-21128074

Available during and outside of office hours.

Independent doctor:

Prof. dr. H.J.M. Verhagen, surgeon Erasmus MC Tel. no.: 010-7040112

Available during office hours.

Complaints:

Secretariaat Klachtenopvang Erasmus MC Tel. no.: 010-7033198

Available during office hours.

P.O. Box: Erasmus MC, attn. secretariaat Klachtenopvang

Antwoordnummer 55, 3000 WB Rotterdam

E-mail: klachtenopvang@erasmusmc.nl

Data Protection Officer of Erasmus MC:

Data Protection Officer Erasmus MC Tel. no.: 010-7034986

Secretariat Department of Legal Affairs

Available during office hours.

For more information about your rights: www.erasmusmc.nl

Erasmus MC
Universitair Medisch Centrum Rotterdam

Appendix B: Subject Consent Form

Effect of music on the clinical outcome after hip fracture operations (MCHOPIN): a multicenter randomized controlled trial

- I have read the subject information form. I was also able to ask questions. My questions have been answered to my satisfaction. I had enough time to decide whether to participate.
- I know that participation is voluntary. I know that I may decide at any time not to participate after all or to withdraw from the study. I do not need to give a reason for this.
- I give permission for my GP to be informed about my participation in this study.
- I give permission for the collection and use of my data and blood to answer the research question in this study.
- I give permission for information to be requested from the nursing home or care home in the way and for the purpose stated in the information sheet.
- I give permission for information to be requested from the hospital pharmacy in the way and for the purpose stated in the information sheet.
- I know that some people may have access to all my data to verify the study. These people are listed in this information sheet. I consent to the inspection by them.
- I consent to my data being stored at the research location (Erasmus MC) for another 15 years after this study.
- I want to participate in this study.

NL64721.078.18 (MCHOPIN study)

Erasmus MC
Universitair Medisch Centrum Rotterdam

Name of the study subject: Date: Signature:	..... __ / __ / __ .....
I hereby declare that I have fully informed this study subject about this study. If information comes to light during the course of the study that could affect the study subject's consent, I will inform him/her of this in a timely fashion.	
Name of investigator (or his/her representative): Date: Signature:	..... __ / __ / __ .....
Additional information was given by	
Name: Job Title: Date: Signature:	.... __ / __ / __ .....

The study subject will receive the full information sheet, together with a copy of the signed consent form

Erasmus MC
Universitair Medisch Centrum Rotterdam

Subject information for participation in medical scientific research

Effect of music on the clinical outcome after hip fracture operations (MCHOPIN): a multicenter randomized controlled trial

Dear Sir/Madam,

You are asked as legal representative to give consent on behalf of your relative/family member to take part in a medical-scientific study (the MCHOPIN study). If a patient is unable to give consent, the legal representative is asked for substitute consent. Participation is voluntary. Participation requires your written consent.

You have received this letter because your relative/family member has broken his/her hip and will undergo surgery. Before you decide whether you want your relative/family member to participate in this study, you will be given an explanation about what the study involves. Please read this information carefully and ask the investigator for an explanation if you have any questions. You can also ask the independent expert, who is mentioned at the end of this document, for additional information. You may also discuss it with your partner, friends or family. Additional information about participating in a study can be found in the enclosed general brochure on medical research.

1. General information

This study has been set up by the Erasmus MC and will be conducted by trauma surgeons in various hospitals in the Netherlands. For this study, 508 study subjects are required. The Medical Research Ethics Committee (MREC) Erasmus MC has approved this study. General information about the assessment of research can be found in the general brochure on medical research.

2. Purpose of the study

Scientific research has shown that music during and around surgery can have a beneficial effect on pain and anxiety. The purpose of this study is to assess the effect of music during and around surgery for a broken hip. Among other things, the effect of music on delirium, pain, anxiety, medication requirement, complications after surgery, stress response of the body, length of hospital stay and / or length of nursing home stay and daily functional ability after surgery will be investigated.

3. Background of the study

It is known that 25-40% of patients with a broken hip in the Netherlands develop delirium, a sudden episode of confusion and disturbance of consciousness. This can lead to other complications after surgery, a prolonged hospitalization and a negative effect on recovery. Therefore, measures are taken to prevent delirium. For example, this is done by treating or reducing risk factors, like pain and stress. Because of the beneficial effect of music on pain and stress, we would like to assess whether music can reduce the occurrence of delirium. The benefit of music compared to other ways of treatment is that it is easy and durable, without side-effects.

4. What participation involves

If your relative/family member participates, participation will last until 3 months after his/her surgery.

Treatment

In this study, half of the subjects will listen to music before, during and after surgery during hospital stay. The other half of the subjects will not listen to music. The music consists of a preselected music list by the investigators, and subjects of the music group will be allowed to choose from this list. It will be determined by drawing lots whether or not your relative/family member will listen to music. Additional information about this can be found in the enclosed general brochure on medical research.

If your relative/family member has drawn the music group, he/she will receive a headphone and listen to music before surgery during 15 minutes. If your

relative/family member is using a hearing aid, he/she will be asked to take it off and to adjust the music volume to a pleasant level. During surgery, your relative/family member will listen to music until leaving the recovery room. After surgery, he/she will listen to music twice a day for 30 minutes during the first 5 days of his/her hospital stay after surgery. If your relative/family member has not drawn the music group, he/she will wear a headphone without music 15 minutes before surgery until leaving the recovery room. He/she is not allowed to listen to music during the first 5 days of his/her hospital stay after surgery, if your relative/family member has not drawn the music group.

Visits and measurements

An additional time investment from the part of your relative/family member is required. During the hospital stay of your relative/family member, he/she will be asked:

- to fill in a pain score once a day, which takes less than 1 minute to complete.
- to fill in once a 6-item questionnaire on his/her level of education, living situation and the role of music in his/her life, which takes approximately 5 minutes to complete.
- to fill in once a 6-item questionnaire on anxiety before and 2 times after surgery, which takes approximately 5 minutes to complete.
- to fill in a 3-item questionnaire on cognition once before surgery. This questionnaire will be administered to your relative/family member by the attending physician or investigator.
- for 2 blood samples to measure the cortisol level, a measurement for the body's stress response. The first sample will be drawn at the start of surgery. For the second blood sample, an extra tubule of blood will be drawn for this study during a routine blood collection after surgery for a broken hip.

During the regular outpatient hospital visit 3 months after surgery, your relative/family member will be asked:

- to fill in once an 8-item follow-up questionnaire on whether or not he/she has been readmitted to hospital, which takes approximately 5 to 10 minutes to complete.
- to fill in once a 6-item questionnaire on daily functional ability, which takes approximately 5 minutes to complete.

Furthermore, the investigator and investigator assistant will collect data from the electronic patient database to answer the research question of this study. This consists of personal data, like age and data on his/her surgical procedure, medication use, complications and hospital stay. If necessary, one of the investigators will contact the hospital pharmacy to assess which medicines your relative/family member received during his/her hospital stay. If your relative/family member stays in a nursing home or care home after discharge from hospital, one of the investigators will contact it for information on the duration of his/her stay.

Other than standard care

If your relative/family member has drawn the music group, he/she will listen to music during and around surgery, both groups will fill in the afore mentioned questionnaires and pain scores and blood will be drawn twice. If your relative/family member has drawn the control group, he/she is not allowed to listen to music during and around his/her surgery and the first five days after his/her surgery, even though he/she might have done this normally. The daily care during hospital stay remains unchanged. This study will end after the regular outpatient hospital visit, 3 months after hospital discharge. No additional study-related visits are required. If no outpatient visit is planned at that time after the operation, one of the investigators will contact you and your relative/family member.

5. What is expected of your relative/family member

In order to carry out the study properly, it is important that your relative/family member follows the study instructions.

The study instructions require that he/she:

- listens to music before, during and the first 5 days after surgery only at the aforementioned moments if he/she has drawn the music group.
- does not listen to music before surgery, during surgery and during the first 5 days after surgery if he/she has not drawn the music group.
- does not participate in another medical study.
- fills in the afore mentioned questionnaires and pain scores, and that twice a tubule of blood will be drawn.

It is important that you contact the investigator:

- if your relative/family member is admitted or treated in an hospital
- if you want your relative/family member to stop participating in this study
- if your contact details or the contact details of your relative/family member change.

6. Possible side effects, complications and discomforts

The music intervention is safe and has no known side effects or complications. To prevent hearing loss, a maximum sound level has been set. Drawing blood can hurt and can lead to bruising in some cases.

7. Possible advantages and disadvantages

It is important that you properly weigh up the possible benefits and disadvantages before you decide for your relative/family member to join. His/her participation can contribute to more knowledge on delirium and the use of music in health care.

Music could potentially have a beneficial effect on delirium, pain and anxiety after surgery, but this is not certain. Disadvantages of participating in this study can be:

- the extra time it will require
- the instructions your relative/family member needs to follow
- that he/she will not be able to listen to music during the first 5 days after surgery
- filling in the questionnaires and pain scores

- drawing of blood

All these aspects have been described above under points 4, 5 and 6.

8. If you do not want your relative/family member to participate or want to stop participation in the study

It is up to you to decide whether or not your relative/family member participates in the study. Participation is voluntary. If you do not want your relative/family member to participate, he/she will be treated as usual for a broken hip. If your relative/family member does participate in the study, you can always change your mind and decide to stop, at any time during the study. He/she will then be treated as usual for a broken hip. You do not have to say why your relative/family member is stopping, but you do need to tell the investigator immediately. The data collected until that time will still be used for the study.

If there is any new information about the study that is important for you, the investigator will let you know. You will then be asked whether you still want your relative/family member to continue participating in this study.

9. Resistance of the person you represent

The person you represent may resist (refuse to cooperate) during the study. The investigator will then have to stop the study immediately. It is difficult to describe what exactly resistance is. Before the start of the study you will be given an explanation of what is considered resistance. The investigator will follow the Code of Conduct on resistance of mentally incompetent and geriatric patients.

10. End of the study

The participation of your relative/family member in the study stops when:

- he/she has completed the outpatient visit and the measurements as described under point 4
- you choose to stop
- the investigator considers it best for your relative/family member to stop

- the sponsor (Erasmus MC), the government or Medical Research Ethics Committee, decides to stop the study.

The study is concluded once all the participants have completed the study.

11. Usage and storage of data and bodily material of your relative/family member

The personal data and bodily material of your relative/family member will be collected, used and stored for this study. This concerns data such as name, address, date of birth and data about health. Also, blood is required for this study. The collection, use and storage of the data and bodily material of your relative/family member are required to answer the questions asked in this study and to publish the results. We ask your permission for the use of the data and bodily material of your relative/family member.

Confidentiality of the data and bodily material of your relative/family member

To protect the privacy of your relative/family member, his/her data and bodily material will be given a code. His/her name and other information that can directly identify your relative/family member will be omitted. Data can only be traced back to your relative/family member with the encryption key. The investigator and investigator assistants are the only people who will know which code your relative/family member has. This is necessary, as they will collect information from the electronic patient database, questionnaires and bodily material. The data and bodily material that is sent to the sponsor will only contain the code, not his/her name or other data with which your relative/family member can be identified. The key to the code will stay with the investigator. The data cannot be traced back to your relative/family member in reports and publications about the study.

Access to the data of your relative/family member for verification

Some people can access all the data of your relative/family member at the research location. Including the data without a code. This is necessary to check whether the study is being conducted in a good and reliable manner. Persons who have access to the data of your relative/family member for

review are members of the research team, a monitor working for the sponsor of the study, and national supervisory authorities, for example, the Healthcare and Youth Inspectorate. They will keep the data of your relative/family member confidential. We ask you to consent to this access.

Retention period of the data and bodily material of your relative/family member

The data of your relative/family member must be kept for 15 years at the research location (Erasmus MC). His/her bodily material will be destroyed immediately after use.

Withdrawing consent

You can withdraw your consent to the use of the personal data of your relative/family member at any time. This applies to this study. The study data collected until the moment you withdraw your consent will still be used in the study. The bodily material of your relative/family member will be destroyed after your consent has been withdrawn. If measurements have already been made with that bodily material, then this data will still be used.

More information about the rights when processing data

For general information about the rights when processing the personal data of your relative/family member, you can consult the website of the Dutch Data Protection Authority.

If you have questions about these rights, please contact the person responsible for the processing of the personal data of your relative/family member. For this study, that is: Erasmus MC. See Appendix A for contact details and website.

If you have questions or complaints about the processing of the personal data of your relative/family member, we advise you to first contact the research location. You can also contact the Data Protection Officer of the Erasmus MC (See Appendix A. Contact details) or the Dutch Data Protection Authority.

Registration of the study

Information about this study is included in a list of medical-scientific studies namely the Dutch trial registry (www.trialregister.nl). It does not contain any information that can be traced to your relative/family member. After the study, the website may display a summary of the results of this study. You can find this study under MCHOPIN.

12. Study subject insurance

This study is not associated with any additional risks for your relative/family member. The MREC Erasmus MC has therefore decided that the sponsor does not need to take out additional insurance.

13. Informing GP and contact with the hospital pharmacy

We will always send the GP of your relative/family member a letter to let them know that he/she is participating in the study. This is for the safety of your relative/family member. If you do not agree to this, your relative/family member cannot participate in this study. Your relative/family member cannot participate in the study if he/she does not have a GP.

During this study, the effect of music on medication use will be assessed. Therefore, the investigators will contact the hospital pharmacy to ask about medication usage. Your relative/family member cannot participate in this study if you do not want this.

14. No Compensation for participation

Participation in this study and use of the sound equipment is free of charge for you and your relative/family member. You and your relative/family member will not be paid for the participation in this study.

15. Any questions?

If you have any questions, please contact the study team. If you would like any independent advice about participation in this study, you may contact the independent doctor. He knows about the study but is not involved in it. If you have any complaints, you may contact the complaint officer at your hospital. All the relevant details can be found in Appendix A: Contact details.

16. Signing the consent form

When you have had sufficient time for reflection, you will be asked to decide on participation of your relative/family member in this study. If you give permission, we will ask you to confirm this in writing on the appended consent form. By your written permission you indicate that you have understood the information and consent to participation of your relative/family member in the study. The signature sheet is kept by the investigator. You will get a copy or a second copy of this consent form.

Thank you for your attention.

17. Appendices to this information

A. Contact details
B. Representative Informed Consent Form
C. Medical Scientific Research Brochure. General Information for Study Subjects (version 01-03-2017)

Erasmus MC
Universitair Medisch Centrum Rotterdam

Appendix A: contact details for Erasmus MC

Principle investigator:

Prof. dr. M.H.J. Verhofstad, trauma surgeon Tel. no.: 010-7031050

Available during office hours. You can contact the general number of the hospital (tel. no. 010-7040704) outside of office hours and ask for the attending of the (trauma)surgery department.

Coordinating investigator:

Mr. V.X. Fu, research physician Erasmus MC Tel. no.: 06-21128074

Available during and outside of office hours.

Independent doctor:

Prof. dr. H.J.M. Verhagen, surgeon Erasmus MC Tel. no.: 010-7040112

Available during office hours.

Complaints:

Secretariaat Klachtenopvang Erasmus MC Tel. no.: 010-7033198

Available during office hours.

P.O. Box: Erasmus MC, attn. secretariaat Klachtenopvang

Antwoordnummer 55, 3000 WB Rotterdam

E-mail: klachtenopvang@erasmusmc.nl

Data Protection Officer of Erasmus MC:

Data Protection Officer Erasmus MC Tel. no.: 010-7034986

Secretariat Department of Legal Affairs

Available during office hours.

For more information about your rights: www.erasmusmc.nl

Erasmus MC
Universitair Medisch Centrum Rotterdam

Appendix B: Representative Informed Consent Form

Effect of music on the clinical outcome after hip fracture operations (MCHOPIN): a multicenter randomized controlled trial

I have been asked to consent to the following person participating in this medical-scientific study:

Name of the study subject: Date of birth:	..... __ / __ / __

- I have read the information sheet for the study subject. I was also able to ask questions. My questions have been answered to my satisfaction. I have had enough time to decide whether this person will participate.
- I know that participation is voluntary. I also know that I can decide at any time that this person will not participate after all. I do not need to give a reason for this decision.
- I give permission for this person's GP to be informed about this person's participation in this study.
- I give permission for the collection and use of data and blood of this person to answer the research question in this study.
- I give permission for information to be requested from the nursing home or care home in the way and for the purpose stated in the information sheet.
- I give permission for information to be requested from the hospital pharmacy in the way and for the purpose stated in the information sheet.
- I know that some people may have access to all the data of this person to verify the study. These people are listed in this information sheet. I consent to the inspection by them.
- I consent to the data being stored at the research location (Erasmus MC) for another 15 years after this study.
- I agree to this person's participation in this study.

NL64721.078.18 (MCHOPIN study)

Name of legal representative: Relationship with the study subject: Date: Signature:	.... __ / __ / __ .....
I hereby declare that I have fully informed this/these person(s) about this study. If information comes to light during the course of the study that could affect the legal representative's consent, I will inform him/her of this in a timely fashion.	
Name of investigator (or his/her representative): Date: Signature:	..... __ / __ / __ .....
Additional information was given by	
Name: Job Title: Date: Signature:	.... __ / __ / __ .....

The representative will receive the full information sheet, together with a copy of the signed consent form

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	3, 18
	2b	All items from the World Health Organization Trial Registration Data Set	18
Protocol version	3	Date and version identifier	18
Funding	4	Sources and types of financial, material, and other support	21, 22
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	21
	5b	Name and contact information for the trial sponsor	N/A
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	21
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	N/A

Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	5, 6
	6b	Explanation for choice of comparators	12, 13
Objectives	7	Specific objectives or hypotheses	6
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	7
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	7
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	8
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	12–14
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	15, 16
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	N/A
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	N/A
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	8–12
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	Figure 1

Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	14, 15
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	15
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	7
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	7
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	17
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	N/A
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	8–12
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	16, 17

Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	15
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	16, 17
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	16, 17
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	16, 17
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	15, 16
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	N/A
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	15, 16
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	N/A
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	18
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	18

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	7
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	N/A
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	15, 16
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	21, 22
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	21, 22
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	15, 16
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	18
	31b	Authorship eligibility guidelines and any intended use of professional writers	18
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	N/A
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Available on request
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	N/A

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.