RESEARCH PROTOCOL

Analysis of lumbar intervertebral motion during flexion and extension cinematographic recordings in asymptomatic male participants

Version 2.0

(September 2018)

TABLE OF CONTENTS

LIST OF ABBREVIATIONS AND RELEVANT DEFINITIONS

AE	Adverse Event
BMI	Body Mass Index
CT	Computer tomography
F-e angle	Flexion-extension angle
IVFE	Intervertebral Flexion-Extension
METC	Medical Research Ethics Committee (MREC); in Dutch: Medische Ethische Toetsingscommissie (METC)
MRI	Magnetic Resonance Imaging
ODI	Oswestry Disability Index (Functional scale used for low back disorders (current version 2a)
ROM	Range Of Motion
(S)AE	(Serious) Adverse Event
TPDR	Translation Per Degree of Rotation
VAS	Visual Analogue Scale
Wbp	Personal Data Protection Act (in Dutch: Wet bescherming persoonsgevens)
WMO	Medical Research Involving Human Subjects Act (in Dutch: Wet Medisch-wetenschappelijk Onderzoek met Mensen)

SUMMARY

Rationale: Physiological motion of the lumbar spine is a subject of interest for doctors and allied health professionals. So far, nobody knows exactly what physiological motion means. Many researchers have described ranges of motion of the lumbar spine, but only a few have mentioned specific motion patterns of each individual segment in healthy individuals. These motion patterns describe the sequence of initiation of segmental motion in rotation during flexion and extension. However, previous studies have not described the sequence of segmental contribution in rotation during flexion and extension.

Objective: Defining the lumbar spines' physiological motion pattern of each vertebra L1, L2, L3, L4, L5 and S1 by using cinematographic recordings in asymptomatic male participants.

Study design: Fundamental research

Study population: Eleven asymptomatic male participants (based on VAS-, and ODI-score of zero) aged 18 to 25 without a medical history of back problems.

Intervention: Two flexion and extension cinematographic recordings of the lumbar spine with a two week interval between recordings.

Main study parameters/endpoints: Primary endpoint: Defining the lumbar spines' physiological motion pattern by analysing sequence of initiation of motion and sequence of segmental contribution in rotation of each vertebra L1, L2, L3, L4, L5 and S1 during flexion and extension.

Secondary endpoint: Exploring the possibility to analyse intervertebral horizontal and vertical translation of each vertebra L1, L2, L3, L4, L5 and S1 during flexion and extension. If mean intra-class correlation coefficient is higher than 0.60 the sequence of initiation of motion and sequence of segmental contribution of intervertebral horizontal and vertical translation will be defined.

Nature and extent of the burden and risks associated with participation, benefit and group relatedness: Participants receive cinematographic recordings twice in two weeks' time, if they are included based on the VAS-, and ODI-scores. There will be no follow-up.

1. INTRODUCTION AND RATIONALE

Physiological motion of the lumbar spine is a subject of interest for medical specialists and allied health professionals. Although the term ‘physiological motion’ is being used in many instances, a proper definition is lacking. More knowledge about physiological motion is essential to recognize abnormal motion caused by specific diseases or complaints.
In 1929 Virchow et al. were first to use sagittal radiographs to analyse normal range of flexion and extension of the cervical spine [1]. Dittmar et al. were the first in 1931 to perform this type of research for the lumbar spine [2]. Troke et al. developed a database with ranges of motion from thoracic vertebra 12 to sacral vertebra 1 for asymptomatic patients between 16 and 90 years old [3]. They found a maximum flexion of 68 to 73 degrees, and a minimum flexion of 40 degrees. For extension they found a maximum of 28 to 29 degrees and minimum of 6 to 7 degrees [3].
After these studies, more (range of) motion research followed, not only using radiographs but later on using CT- or MRI-based 3D images [4-6]. The latest studies described individual motions of segments and initiation of motion in flexion and extension. However, none of these studies have described a number of important aspects we would like to consider in our study. These aspects include description of flexion and extension of each individual participant instead of pooled data for the entire group, extension analysis and sequence of segmental contribution besides sequence of initiation of motion per segment during flexion and extension.

By addressing these specific aspects, our study aims to assess and understand the sequence of initiation of motion in each individual segment and the sequence of segmental contribution in rotation of the lumbar spine, during maximum flexion and extension in asymptomatic male participants, in order to learn more about physiological motion of the lumbar spine. Additionally, we want to explore the possibility of analysing intervertebral horizontal and vertical translation to enable determination of sequence of initiation of motion and sequence of segmental contribution of translation.
Eventually, we hope to compare this physiological motion to potential abnormal motion in patients suffering from lumbar spinal pathology or postoperative patients, for example after fusion surgery, to determine if (adjacent) segments have to contribute more in flexion and extension, which could explain (adjacent segment) diseases due to abnormal segmental motion patterns.

2. OBJECTIVES

Primary Objective: Defining the lumbar spines' physiological motion by analysing sequence of initiation of motion and sequence of segmental contribution in rotation of each vertebra L1, L2, L3, L4, L5 and S1 by using flexion and extension cinematographic recordings in asymptomatic male participants.

Secondary objective: Exploring the possibility to analyse intervertebral horizontal and vertical translation of each vertebra L1, L2, L3, L4, L5 and S1 by using flexion and extension cinematographic recordings in asymptomatic male participants. If mean intra-class correlation coefficient is higher than 0.60, sequence of initiation of motion and sequence of segmental contribution of intervertebral horizontal and vertical translation will be analysed.

3. STUDY DESIGN

This is a fundamental research project in which asymptomatic male participants without any medical history of back pain will be included. Participants will be recruited at Zuyd Hogeschool Sittard/Heerlen and Zuyderland Medical Center Sittard-Geleen/Heerlen by using posters notifying about the study. Males interested in participation can email the researcher, which will inform them verbally and in writing. Informed consent will be signed if males meet the inclusion criteria and are willing to participate.
During our literature research we came across studies confirming the feasibility of sagittal cinematographic recordings in analysing flexion and extension of the lumbar spine [7-9]. For this reason, we decided not to perform a feasibility study, but to include 11 male participants based on previous articles using the same method of cinematographic recordings to analyse motion of the spine. Boselie et al., Kanayama et al. and Harada et al. have used eight to ten participants and were able to perform adequate analysis and draw solid conclusions [7-9]. Interim analysis will be performed after cinematographic recordings of two patients to determine if the images acquired with the Alura Xper are appropriate to perform computer software analysis. Taking a possible loss to follow up of 10% into account, our study population will consist of 11 participants.
Each participant receives a flexion and extension cinematographic recording twice to determine reproducibility and consistency of sequence between the two time points (T1 and T2) [10, 11]. Recordings will be done with an interval of two weeks (T1 and T2), resulting in 22 cinematographic recordings. Inclusion is expected to take approximately three months. Possible participants have to complete the Oswestry Disability Index and Visual Analogue Scale for back pain with a score of zero to be included. Cinematographic recordings will be scored based on the Kellgrens' classification by two neurosurgeons to avoid inclusion of participants with asymptomatic degeneration. This score has to be zero or one meaning there is no or 'doubtful' degeneration. Participants with a Kellgrens' score of two or higher, indicating possible degeneration of the spine, will be excluded [12].

4. STUDY POPULATION

4.1. Population

Male participants with a normal height-weight ratio (BMI under 25), without spinal problems defined as ODI-, and VAS-scores of zero, and without a medical history of visiting general practitioners, allied health professionals, or medical specialists for spinal problems.
We exclude females from participation to protect ovaries from direct radiation exposure. Previous studies did not show significant differences in motion between males and females. Lower radiation dosage for proper cinematographic recordings is needed if males have a BMI under 25.
Participants will be recruited using posters shown in Zuyd Hogeschool Sittard/Heerlen and Zuyderland Medical Center Sittard-Geleen/Heerlen.

4.2. Inclusion criteria

To be included in the study, participants have to meet the following criteria:
1. Male
2. Age between 18 and 25 years old.
3. BMI under 25
4. Participants have to be able to perform flexion and extension over a full range of motion without complaints of pain.
5. Participants have no medical history of spinal problems based on anamneses and an ODI-, and VAS-score of zero.
6. Kellgrens' classification on cinematographic recordings is zero or one.
7. Signed informed consent.
8. Ability to read and understand Dutch.

4.3. Exclusion criteria

To be excluded from the study, participants have to meet the following criteria:
1. Medical history of visiting general practitioners, allied health professionals or specialists for spinal problems.
2. Former spine surgery.
3. Radiographs of abdomen, pelvis, hips, lumbar spine or sacral spine in last year.
4. Degenerative abnormalities of the lumbar spine.
5. Active spinal infection.
6. Immature bone.
7. Lumbar tumour processes.
8. Former lumbar radiotherapy.
9. Congenital lumbar spine abnormalities, for example spina bifida.
10. Planning pregnancy for the coming year.

4.4. Sample size calculation

Sample size is based on previous articles using the same method of cinematographic recordings to analyse spine motion. Boselie et al., Kanayama et al. and Harada et al. used eight to ten participants to perform adequate analysis and draw solid conclusions [7-9]. Our study population comprises 11 participants, assuming a possible loss to follow-up of 10%. Flexion and extension cinematographic recordings are acquired twice for each participant, in order to determine reproducibility and consistency of sequence of motion between two time points (T1 and T2) [10]. Recordings will be performed with an interval of two weeks, resulting in 22 cinematographic recordings.

5. TREATMENT OF SUBJECTS

5.1. Investigational product/treatment

Cinematographic recordings during flexion and extension of the lumbar spine in asymptomatic male participants.

5.2. Use of co-intervention

Not applicable.

5.3. Name and description of investigational product(s)

Not applicable.

5.4. Summary of findings from non-clinical studies

Not applicable.

5.5. Summary of findings from clinical studies

- Pearcy (1984): Mean range of flexion for healthy participants (n=11) was 8º for L1-L2, 10º for L2-L3, 12º for L3-L4, 13º for L4-L5 and 9º for L5-S1. Mean range of extension was 5º for L1-L2, 3º for L2-L3, 1º for L3-L4, 2º for L4-L5 and 5º for L5-S1. Mean cumulated range for flexion and extension in L4-L5 is significant higher compared to segments above [13].
- Dvorak (1991): Healthy participants (n=41) performed passive flexion and extension. Ranges of motion from flexion to extension were 11.9^o in L1-L2, 14.5^o in L2-L3, 15.3^o in L3-L4, 18.2^o in L4-L5 and 17.0^o in L5-S1. Segmental rotation was higher in lower levels, but variation of these values was also higher. There was no statistically significant difference between levels and genders [14].
- Kanayama (1996): Segmental translation of healthy participants (n=8) during flexion was smaller in L5-S1 (1.1 mm) compared to L3-L4 (3.1 mm) and L4-L5 (3.3 mm) ($P<0.001$). Segmental rotation was largest in L4-L5 (15.3^o) and smallest in L3-L4 (9.8^o) ($P<0.05$). There was no significant difference between individual levels in segmental translation during extension. Segmental rotation was smaller in L3-L4 (1.6^o) and L4-L5 (0.6^o) compared to L5-S1 (8.5^o) ($P<0.05$). L3-L4 and L4-L5 had significantly smaller translation and rotation during extension compared to flexion ($P<0.05$ and $P<0.005$, respectively). Translation and rotation were not significantly smaller during flexion and extension in L5-S1.
  Flexion started in L3-L4, continued to L4-L5 when L3-L4 had rotated 6^o and ended with rotation of L5-S1 when L3 to L5 had rotated 8^o [8].
- Okawa (1998): Two motion patterns were observed in healthy participants (n=13) during flexion from neutral position. One involved sequential lumbar segmental rotation starting from L2 and spreading gradually downward to L4. The other involved simultaneous motion-spreading pattern with motion curves of L2 to L4, except L5, showing almost the same course. Of 13 healthy participants, six exhibited a sequential motion-spreading pattern, four exhibited the simultaneous pattern and in three patients the segments did not move in any of the abovementioned orders. Six of

eight patients with chronic low back pain showed a sequential or simultaneous pattern. In seven of the eight patients with spondylolisthesis, the slipped level seemed to move first.
Three motion patterns were observed when participants returned from flexion to neutral position. In one pattern, all segments returned simultaneously to normal position. In the other two patterns, lower segments returned earlier than upper segments (low-high type) or upper segments returned earlier than lower segments (high-low type). Seven out of eight patients with spondylolisthesis showed high-low type motion, most of all with prolonged deflection of the slipped L4, which was defined as ‘abnormal’. Most patients with ‘normal’ motion tended to have low-high type [15].

- Harada (2000): Healthy male participants (n=10) were trained to perform maximum flexion and extension each in six seconds, which were recorded by cinematographic recordings at a rate of 30 frames/second. Flexion started in L3-L4 and continued step-by-step to lower segments. Extension started in L5-S1 and continued step-by-step to higher segments. Rate for change of angle improved significantly with each lower segment during initiation of flexion; 3.9±1.5 in L3-L4, 5.4±2.3 in L4-L5 and 8.1±2.1 in L5-S1 in grades per second. There was no significant difference between segments regarding rates for change of angle during start of extension. Greatest angle changes were -6.3±2.5 in L3-L4, -7.5±2.8 in L4-L5 and -7.3±2.8 in L5-S1 in grades per second [9].
- Takayanagi (2001): Healthy participants (n=20) showed a simultaneous start in segments L2 to L5 for f-e angle (flexion-extension angle) and translation. Segment L5-S1 showed initial delay. F-e angle and translation changed symmetrically between segments. Patients with spondylolisthesis L4-L5 with a slip less than 15% (n=21) showed a larger change of f-e angle in this segment than healthy individuals, indicating disc dysfunction. Patients with spondylolisthesis L4-L5 with a slip over 15% (n=20) showed less change of f-e angle and translation than healthy individuals, supporting the identification of the restabilization stage in degenerative processes [16].
- Lee (2002): L1-L2, L2-L3, L3-L4, L4-L5 and L5-S1 of healthy participants (n=30) showed a steady increase and linear pattern of the intervertebral flexion-extension (IVFE) curve from 10^{o} extension to 40^{o} flexion (except for L5-S1 for 10^{o} extension). IVFE decreased in the descending order of L1-L2 to L5-S1 at all points of flexion. There was no statistically significant difference in slope of IVFE curves in different ROMs between genders [17].
- Wong (2004): Results of healthy participants (n=100) showed a linear-liked motion pattern of IVFE with alignment of L2-L3 curve with L3-L4 curve during flexion. (The slope of) IVFE curves decreased from L1-L2 to L5-S1 in descending order, suggesting less flexibility in lower levels. Initiating of flexion starts in upper segments and continues to lower segments, but all segments initiated extension simultaneously. Extension-slope for L5-S1 was less steep than the rest. Increased IVFE was found in flexion and extension for older participants compared to younger participants. The

slope of the IVFE curve was significantly steeper in the oldest group compared to younger groups in all levels (P<0.05). There was no statistically significant difference between genders [18].
- Wong (2006): IVFE curves and slopes of healthy participants (n=30) showed a decreased linear pattern in descending order from L1-L2 to L5-S1 during flexion, but motion is unevenly contributed. Extension is evenly contributed. There was no statistically significant difference between genders [19].
- Wu (2014): Anterior-posterior translation in healthy participants (n=10) showed significantly more horizontal translation in segment L4-L5 than in segment L5-S1, respectively, 2.9±1.5 versus 1.4±1.1 mm. Vertical translation was 1.5±0.4 mm in L2-L3, 1.0±0.4 mm in L3-L4, 1.7±0.7 mm in L4-L5 and 2.8±0.9 mm in L5S1. Largest proximal-distal translation was found in segment L5-S1, 2.8±0.9 mm. Rotation in L2 relative to S1 was 29.8°±8.2° from maximum flexion to maximum extension [20].
- Staub (2015): Individual segments of healthy participants (n=162) showed a translation of 1.88 mm in L1-L2, 2.42 mm in L2-L3, 2.69 mm in L3-L4, 2.66 mm in L4-L5 and 0.53 mm in L5-S1. Intervertebral rotation of individual segments was 12.38° in L1-L2, 12.38° in L2-L3, 13.02° in L3-L4, 14.45° in L4-L5 and 12.72° in L5-S1. Translation per degree of rotation (TPDR) at every level was 0.55%, except for L5-S1 were TPDR was 0.18% [12].
- Boselie (2017): Consistent sequence of contribution of sagittal rotation of the three lower cervical motion segments C4-C7 was especially identified in the last phase of extension movement in healthy participants (n=20). First peak was found for C4-C5, followed by C5-C6 and finally in C6-C7. This sequence was only present in 10% of all participants (n=10) with cervical degenerative disc disease [10].

Above-mentioned small scaled studies provide information about translation and rotation of lumbar spine segments from L1 to S1. Extension seems to be correlated to a smaller translation and range of motion compared to flexion, where most studies describe segment L5-S1 as least mobile.

Kanayama et al., Wong et al., Lee et al., Takayanagi et al., Okawa et al. and Harada et al. described motion of individual segments L1/2/3 to S1 [8, 9, 16-19]. Wong et al., Lee et al., Takayanagi et al., and Harada et al. only mentioned means of the study population, whereas Kanayama et al. and Okawa et al. mentioned individuals separately. All studies described sequence of onset of motion, but not sequence of segmental contribution. They all described cumulative rotation of each individual segment on specific time points or at specific lumbar ROMs', which can result in missing drastic changes in intervertebral rotation between successive frames. Besides, Kanayama et al., Takayanagi et al. and Okawa et al. only described flexion, not extension [8, 15, 16]. Wong et al. and Lee et al. limited flexion to 40° and extension to 10° [17-19].

We want to describe segmental contribution during maximum flexion and extension in asymptomatic participants. Eventually, we hope to compare this physiological motion to potential abnormal motion in patients suffering from lumbar spinal pathology or postoperative patients, for example after fusion surgery, to determine if (adjacent) segments have to contribute more in flexion and extension, which could explain (adjacent segment) diseases due to abnormal segmental motion patterns.

5.6. Summary of known and potential risks and benefits

Based on the above-mentioned studies, there is no information on potential risks or benefits. Radiation experts determined a radiation dosage per cinematographic recording of 0.21 mSv. Participants will perform cinematographic recordings twice, resulting in a total radiation dosage of 0.42 mSv. This amount of radiation can be categorized in category IIa using the NCS guidelines about risks of radiation dosage (0.1 to 1 mSv) [21]. This category includes moderate risk which can be justified if there is a potential health benefit for future patients.

6. METHODS

6.1. Study parameters/endpoints

6.1.1. Main study parameter/endpoint

Defining the lumbar spines' physiological motion pattern by analysing sequence of initiation of motion and sequence of segmental contribution in rotation of each vertebra L1, L2, L3, L4, L5 and S1 by using flexion and extension cinematographic recordings in asymptomatic male participants.

6.1.2. Secondary study parameter/endpoint

Secondary objective: Exploring the possibility to analyse intervertebral horizontal and vertical translation of each vertebra L1, L2, L3, L4, L5 and S1 by using flexion and extension cinematographic recordings in asymptomatic male participants. If mean intra-class correlation coefficient is higher than 0.60, the sequence of initiation of motion and sequence of segmental contribution of intervertebral horizontal and vertical translation will be analysed.

6.2. Randomization, blinding and treatment allocation

Not applicable.

6.3. Study procedures

This study does not use invasive procedures, but is not regular care:

- Cinematographic recordings (twice): participants are seated while their pelvis is fixated by belts to prevent additional pelvic motion. Cinematographic recordings will be made from a lateral perspective to obtain sagittal images. Participants are asked to perform maximum extension, followed by maximum flexion and returning to maximum extension. Cinematographic recordings will be made twice with an interval of two weeks.
  Cinematographic recordings will be made using the Philips Alura Xper FD20 X-ray system. To stay below the limit of 1 mSv per participant, the 0.9 mm Cu + 1 mm Al filter will be used for the entire study. The Alura Xper automatically selects correct tube voltage, with an expected maximum between 75 and 90 kV for lumbar cinematographic recordings. Kellgrens' classification of cinematographic recordings will be determined by two neurosurgeons.
- Questionnaires for inclusion:
    - VAS (Visual Analogue Scale) Back
    - VAS (Visual Analogue Scale) Leg
    - ODI (Oswestry Disability Index)

Kellgrens' classification: a scoring method to determine severity of osteoarthritis in joints, using five gradations:

- Grade zero: no radiological abnormalities indicating osteoarthritis.
- Grade one: discussable joint space narrowing and beginning of osteophyte formation.
- Grade two: clear joint space narrowing and osteophyte.
- Grade three: joint space narrowing, multiple osteophytes, sclerosis and bone deformity.
- Grade four: joint space narrowing, large and multiple osteophytes, severe sclerosis and bone deformity [22].

Visual Analogue Scale: back pain and leg pain will be indicated on a scale of 100 points were zero points represents no pain and hundred points represents worst pain imaginable [23].

Oswestry Disability Index: tool to measure functional invalidity of patients with low back problems. ODI-questionnaire consists of ten questions. Each question will be scored between zero and five points. A total of zero points stands for no invalidity and a total of 50 points for worst invalidity imaginable [24].

6.4. Withdrawal of individual subjects

Participants can cease study participation at any time for any reason if they wish to do so, without any consequences. If participants leave the study before second recording, only the first recording will be included and analysed.
Researchers cannot decide to withdraw participants from the study, unless participants do not respond to calls before the first cinematographic recording is made.

6.5. Replacement of individual subjects after withdrawal

If a participant withdraws before the first cinematographic recording is made, researchers are allowed to replace this participant.

6.6. Follow-up of subjects withdrawn from treatment

Participants who withdraw from the study will not be actively recalled.

6.7 Premature termination of the study

Interim analysis will be performed after cinematographic recordings of two patients to determine if the image quality with the maximum allowable settings of the Alura Xper have sufficient quality and are appropriate to perform computer software analysis. If this is not possible, the study will be terminated prematurely.

7. SAFETY REPORTING

7.1. Section 10 WMO event

In accordance to section 10, subsection 4, of the WMO, sponsor and investigator will inform the participant and the METC if there is sufficient ground that continuation of the study will jeopardize participants' health or safety. The study will be suspended pending further review by the accredited METC.

7.2. AEs and SAEs

7.2.1. Adverse events (AEs)

Adverse events are defined as any undesirable experience occurring to a participant during the study, whether or not considered related to experimental intervention. All adverse events reported spontaneously by participant or observed by the investigator or his staff will be recorded.

7.2.2. Serious adverse events (SAEs)

A serious adverse event is any untoward medical occurrence or effect that results in
- Death;
- Is life threatening (at the time of event);
- Requires hospitalization or prolongation of existing inpatients' hospitalization;
- Results in persistent or significant disability or incapacity;
- Is a congenital anomaly or birth defect;

That required medical or surgical intervention to preclude of any other important medical event that did not result in any of the outcomes listed above due to medical or surgical intervention but could have been based upon appropriate medical judgment.

An elective hospital admission will not be considered as a serious adverse event. The investigator will report all SAEs to the sponsor without undue delay of obtaining knowledge of the events.

Sponsor will report these SAEs through the web portal *ToetsingOnline* to the accredited METC that approved the protocol, within 7 days for SAEs that result in death or life threatening event, followed by a period of maximum of 8 days to complete the initial preliminary report. All other SAEs will be reported within a period of maximum 15 days after sponsor has first knowledge of the serious adverse events.

7.3. Follow-up of adverse events

All AEs will be followed until they have abated, or until a stable situation has been reached. Depending on event, follow up may require additional tests or medical procedures as indicated, and/or referral to general physician or medical specialist. SAEs need to be reported till end of study (last follow up moment for last subject), as defined in the protocol.

8. STATISTICAL ANALYSIS

8.1. Primary study parameter(s)

Primary study parameter is to define the lumbar spines' physiological motion by analysing sequence of initiation of motion and sequence of segmental contribution in rotation of each vertebra L1, L2, L3, L4, L5 and S1 by using flexion and extension cinematographic recordings in asymptomatic male participants.

Before recordings are made, participants will be taught to perform the prescribed motion over 14 seconds using a metronome. Participants are seated with their pelvis fixated during sagittal cinematographic recordings and are asked to perform maximum extension, followed by maximum flexion and returning to maximum extension. Participants perform this procedure twice with an interval of two weeks. If segment L1 does not remain in the field of view, we will start analysing downwards from segment L2.

Images will be analysed using computer software that uses an algorithm to follow motion of the vertebrae during complete flexion and extension [25]. This will be done by two researchers for 10 cinematographic recordings to determine reproducibility using two way mixed, absolute agreement, intra-class correlation coefficient.

Graphs will be made for flexion and extension in which segmental rotation (cumulative and between each pair of successive frames) of each individual segment L1 to S1 will be plotted against the cumulative rotation in segments L1 to S1 together to describe the sequence of segmental contribution during flexion and extension. These graphs will be made and analysed for each individual participant to identify specific patterns in sequence of segmental contributions. If possible, we will describe a sequence definition for initiation of motion and segmental contribution in flexion and extension of the lumbar spine. This above-mentioned procedure will first be done for T1, which will be tested against T2 using coefficient of variation and intra-individual standard deviation to determine if the defined sequence is consistent between two recordings in the intra-individual variability.

8.2. Secondary study parameter(s)

Secondary parameter is to explore the possibility to analyse intervertebral horizontal and vertical translation of each vertebra L1, L2, L3, L4, L5 and S1 by using flexion and extension cinematographic recordings in asymptomatic male participants. Previous studies of the cervical spine described the possibility to determine intervertebral horizontal and vertical translation, with an intra-class correlation coefficient higher than 0.60 [26]. However, a few previous studies of the lumbar spine described pooled data for intervertebral horizontal translation and/or only for specific parts of the flexion-extension motion. Only one study described vertical translation [8, 12, 13, 20, 27].

To explore the possibility to analyse intervertebral horizontal and vertical translation of the lumbar spine for each individual participant, we use the same procedure for recording and computer-analysis as mentioned above. If mean intra-class correlation coefficient is higher than 0.60, sequence of initiation of motion and sequence of segmental contribution of intervertebral horizontal and vertical translation will be determined.

8.3. Interim analysis

Interim analysis will be performed after cinematographic recordings of two patients to determine if the image quality with the maximum allowable settings the Alura Xper have sufficient quality and are appropriate to perform computer software analysis. These filter and tube voltage settings are used for lumbar cinematographic recordings in daily practice and will not overstep the limit for radiation dosage of 1 mSv per participant. If appropriate computer software analysis is not possible, the study will be stopped.

.

9. ETHICAL CONSIDERATIONS

9.1. Regulation statement

This research is conducted according to principles enshrined in the Declaration of Helsinki (3^{th} edition 2013) and in accordance with the Medical Research Involving Human Subjects Act (WMO, version 1 July 2012).

9.2. Recruitment and consent

Male participants will be recruited from Zuyd Hogeschool Sittard/Heerlen and Zuyderland Medical Center Sittard-Geleen/Heerlen using posters. Possible participants have to send an email to the researcher if they are interested in participation. Further information will be given verbally and in writing, followed by a thinking time of seven days. If people are willing to participate and meet the inclusion criteria, informed consent will be signed during the first meeting between researcher and participant.
Participants can terminate their participation at all times, without giving a reason. For any questions regarding the study, an independent physician is available throughout the duration of the study.

9.3. Objection by minors or incapacitated subjects

Not applicable.

9.4. Benefits and risks assessment, group relatedness

Participants do not directly benefit from participating in this study. They make significant contribution to knowledge in the field of motion of the lumbar spine. Increased knowledge of physiological motion enables us to recognize abnormal motion in future.
Phantom measurements of the Alura Xper in Zuyderland Sittard were used to determine radiation dosage. According to radiation experts, radiation dosage per cinematographic recording will be 0.21 mSv. Settings used for calculation are exposed tissue factor of 0.54 mSv/Gy (based on ICRP 103), tube voltage of 75-90 kV, record-duration of 20 seconds, filter of 0.9 mmCu + 1 mm Al, 7.5 pulses per second, focus-detector distance of 48 cm and field of view of 520 cm^2. Participants will perform cinematographic recordings twice, resulting in a total radiation dosage of 0.42 mSv. This amount of radiation can be categorized in category IIa using the NCS guidelines about risks of radiation dosage (0.1 to 1 mSv) [21]. This category includes moderate risk which can be justified if there is a potential health benefit for future patients.
We exclude females from participation to protect ovaries from direct radiation exposure. Lower radiation dosage for proper cinematographic recordings is needed if males have a BMI under 25.

9.5. Compensation for injury

Sponsor/researcher has a liability insurance which is in accordance with article 7 of the WMO. This insurance provides cover for damage to research participants through injury or death caused by the study.

9.6. Incentives

Participants will be reimbursed for extra time that is needed to fill out the questionnaires and undergo cinematographic recordings. They will receive €50 for participating in T1 and T2.

10. ADMINISTRATIVE ASPECTS, MONITORING AND PUBLICATION

10.1. Handling and storage of data and documents

Data will be stored in two ways; cinematographic recordings on CDs and questionnaires on paper. Both of them will be coded with participant-number for example participant 9. Cinematographic recordings will also be coded with recording-number, for example recording 2. CDs and questionnaires will be locked up in a secured room. Data will be kept for 15 years after ending the study. Handling of personal data will comply with the Dutch Personal Data Protection Act (Wbp).

10.2. Monitoring and Quality Assurance

Monitoring will be performed by trained and qualified monitors. According to Good Clinical Practice (GCP) guidelines main task of the monitor is ensuring that:

- Rights and well-being of human participants are protected.
- Reported trial data are accurate, complete and verifiable from source documents.
- Conduct of trial is in compliance with currently approved protocol, GCP and applicable regulatory requirements.
- Prior to the study start a monitoring plan will be assembled, specifying Source Document Verification Plan, frequency of monitoring visits and frequency of checking Trial Master Files/Investigator Site Files.

Monitoring will be performed remotely and on site.

There are several kinds of monitoring visits:

- Site initiation visit (SIV): SIV will be performed after all approvals have been obtained and prior to enrolling the first subject in that center.
- Interim monitoring visit (IMV): Several IMV’s will be performed during the trial. Frequency of visits is determined in monitoring plan.
- Close out visit (COV): COV will be performed at the end of the trial, after collection of all data.

Monitoring visits will be planned in agreement with study site personnel. According to GCP guidelines, the investigators must provide the monitor with all necessary information and documents. Furthermore, the investigators are obliged to answer all queries raised by monitor in eCRF in timely manner. After each monitoring visit, a follow-up email with all action points will be sent to the study site. These action points will be addressed at beginning of the next monitoring visit.

10.3. Amendments

Amendments are changes made to the research after a favourable opinion by the accredited METC has been given. All amendments will be notified to the METC that gave a favourable opinion.

10.4. Annual progress report

Sponsor/researcher will submit a summary of progress of the trial to the accredited METC once a year. Information will be provided on date of inclusion of the first subject, numbers of subjects included and numbers of subjects that have completed the trial, serious adverse events, other problems, and amendments.

10.5. Temporary halt and (prematurely) end of study report

Sponsor/researcher will notify the accredited METC of the end of the study within a period of 8 weeks. The end of the study is defined as the last participants' last visit.
Sponsor/researcher will notify METC immediately of a temporary halt of the study, including reason of such an action.
In case of ending the study prematurely, sponsor/researcher will notify the accredited METC within 10 days, including reasons for premature termination.
Within one year after the end of the study, sponsor/researcher will submit a final study report with results, including any publications/abstracts, to the accredited METC.

10.6. Public disclosure and publication policy

This trial will be registered in a public trial register before recruitment of the first participant. Results will preferable be published in open access, peer-reviewed journals. Data of participants will be anonymous for publication and cannot be traced to an individual. In case of negative results, data will also be published. Funder has through contractual agreement no effect on publication. There is no veto over whether or not to publish data by one of the parties. In case of patent applications, funder is entitled to postpone publication for a maximum period of 90 days after analysing data.

11. STRUCTURED RISK ANALYSIS

Not applicable.

12. REFERENCES

1. H., V., *Die saggitale flexorische Bewegung der Menschlichen Halswirbelsäule.* Arch Orthop Unfallchir, 1928. **26**: p. 1-42.
2. O., D., *Roentgenstudien zur Mechanologie der Wirbelsäule.* Z Orthop, 1931. **55**: p. 321-351.
3. Troke, M., et al., *A normative database of lumbar spine ranges of motion.* Man Ther, 2005. **10**(3): p. 198-206.
4. P. Svedmark, T.T., G. Q. Maguire Jr., L. Weidenhielm, M. E. Noz, M. P. Zeleznik, G. Nemeth, H. Olivecrona, *Three-dimensional movements of the lumbar spine facet joints and segmental movements: in vivo examinations of normal subjects with a new non-invasive method.* 2012. **21**: p. 599 - 605.
5. J.R. JINKINS, J.S.D., C.A. GREEN, J.N GREENHALGH, M. GIANNI, M. GELBIEN, R.B.WOLF, J. DAMADIANX. R.V DAMADIAN, *Upright, Weight-Bearing, Dynamic-Kinetic MRI of the spine pMRI/kMRI.* Rivist di Neuroradiologia, 2002. **15**: p. 333 - 356.
6. Christopher M. Powers, K.K., James Harrison, Gabrielle Bergman, *Segmental mobility of the lumbar spine during a posterior to anterior mobilization: assessment using dynamic MRI.* Clinical Biomechanics, 2003. **18**: p. 80 - 83.
7. Boselie, T.F., et al., *Cervical spine kinematics after anterior cervical discectomy with or without implantation of a mobile cervical disc prosthesis; an RCT.* BMC Musculoskelet Disord, 2015. **16**: p. 34.
8. Kanayama, M., et al., *Phase lag of the intersegmental motion in flexion-extension of the lumbar and lumbosacral spine. An in vivo study.* Spine (Phila Pa 1976), 1996. **21**(12): p. 1416-22.
9. Harada, M., et al., *Cineradiographic motion analysis of normal lumbar spine during forward and backward flexion.* Spine (Phila Pa 1976), 2000. **25**(15): p. 1932-7.
10. Boselie TFM, v.S.H., de Bie RA, van Mameren H., *Pilot Study of Sequence of Segmental Contributions in the Lower Cervical Spine During Active Extension and Flexion: Healthy Controls Versus Cervical Degenerative Disc Disease Patients.* Spine (Phila Pa 1976), 2017. **42**(11): p. 642 - 647.
11. H. Van Mameren, J.D., H. Sanches, J. Beurgens, *Cervical Spine Motion in the Sagittal Plane (I); Range of Motion of Actually Performed Movements, an X-ray Cinematographic Study.* European Journal of Morphology, 1990. **28**(1): p. 47 - 68.
12. Staub, B.N., et al., *Sagittal plane lumbar intervertebral motion during seated flexion-extension radiographs of 658 asymptomatic nondegenerated levels.* J Neurosurg Spine, 2015. **23**(6): p. 731-8.
13. Pearcy, M., I. Portek, and J. Shepherd, *Three-dimensional x-ray analysis of normal movement in the lumbar spine.* Spine (Phila Pa 1976), 1984. **9**(3): p. 294-7.
14. j. Dvorak, M.M.P., G. Chang, R. Theiler, D. Grob, *Functional Radiographic Diagnosis of the Lumbar Spine.* SPINE, 1991: p. 562 - 571.
15. Atsushi Okawa, K.S., Hiromichi Komori, Takeshi Muneta, Yoshiyasu Arai, Osamu Nakai *Dynamic Motion Study of the Whole Lumbar Spine by Videofluoroscopy.* SPINE, 1998. **23**(16): p. 1743 - 1749.
16. Kenji Takayanagi, K.T., Masatsune Yamagata, Hideshige Moriya, Hiroshi Kitahara, Tamotsu Tamaki, *Using Cineradiography for Continuous Dynamic-Motion Analysis of the Lumbar Spine.* SPINE, 2001. **26**(17): p. 1858 – 1865.
17. Sai-wing Lee, K.W.N.W., Man-kwong Chan, Hon-ming Yeung, Jeffrey L. F. Chiu, John C. Y. Leong, *Development and Validation of a New Technique for Assessing Lumbar Spine Motion.* SPINE, 2002. **27**(8): p. 215 - 220.
18. Kris W.N. Wong, J.C.Y.L., Man-kwong Chan, K.D.K. Luk, W.W. Lu, *The Flexion-Extension Profile of Lumbar Spine in 100 Healthy Volunteers.* SPINE, 2004. **29**(15): p. 1636 - 1641.
19. Kris W.N. Wong, K.D.K.L., John C.Y. Leong, S.F. Wong, Kenneth K.Y. Wong, *Continuous Dynamic Spinal Motion Analysis.* SPINE, 2006. **31**(4): p. 414 - 419.
20. Wu, M., et al., *Dynamic motion characteristics of the lower lumbar spine: implication to lumbar pathology and surgical treatment.* Eur Spine J, 2014. **23**(11): p. 2350-8.

21. Dosimetry, N.C.o.R., *Human Exposure to Ionising Radioation for Clinical and Research Purposes: Radioation Dose & Risk Estimates.* 2016.
22. Kellgren, J.H. and J.S. Lawrence, *Radiological assessment of osteo-arthrosis.* Ann Rheum Dis, 1957. **16**(4): p. 494-502.
23. Hawker, G.A., et al., *Measures of adult pain: Visual Analog Scale for Pain (VAS Pain), Numeric Rating Scale for Pain (NRS Pain), McGill Pain Questionnaire (MPQ), Short-Form McGill Pain Questionnaire (SF-MPQ), Chronic Pain Grade Scale (CPGS), Short Form-36 Bodily Pain Scale (SF-36 BPS), and Measure of Intermittent and Constant Osteoarthritis Pain (ICOAP).* Arthritis Care Res (Hoboken), 2011. **63 Suppl 11**: p. S240-52.
24. Fairbank, J.C. and P.B. Pynsent, *The Oswestry Disability Index.* Spine (Phila Pa 1976), 2000. **25**(22): p. 2940-52; discussion 2952.
25. Reinartz, R., et al., *Cervical vertebrae tracking in video-fluoroscopy using the normalized gradient field.* Med Image Comput Comput Assist Interv, 2009. **12**(Pt 1): p. 524-31.
26. Shyi-Kuen Wu, J.-Y.J., Hsin-Min Lee, Han-Yu Chen, Fong-Chin Su, Li-Chieh Kuo, *The reproducibility comparison of two intervertebral translation measurements in cervical flexion-extension.* The Spine Journal, 2015. **15**: p. 1083–1091.
27. Ameet K. Aiyangar, L.Z., Scott Tashman, William J. Anderst, Xudong Zhang, *Capturing Three-Dimensional In Vivo Lumbar Intervertebral Joint Kinematics Using Dynamic Stereo-X-Ray Imaging.* Journal of Biomechanical Engineering, 2014. **136**.