TEMPLATE RESEARCH PROTOCOL

(September 2018)

- May 2015: adaptation section 11.5: text in accordance to old and new Measure regarding Compulsory Insurance for Clinical Research in Humans
- Sept 2015: adaptation section 9.1, 9.2 and 12.5: text in accordance to WMO amendment on reporting SAE and temporary halt (section 10 of WMO)
- Oct 2015: adaptation section 4.4 – comment [CCMO15], 8.2 and 10.1 with respect to methodology/statistics
- Sept 2018: adaptation section 12.1 and comment [CCMO46] due to applicability GDPR as of May, 2018

PROTOCOL TITLE 'Prospective Hounsfield Unit measurements of intercorporal bone grafts remodelling towards spinal fusion'.

Protocol ID	***NL81678.091.22***
Short title	**Intercorporal Bone Graft Measurement Study**
EudraCT number	**N/A**
Version	**4**
Date	**09-09-2022**
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	Antwoordnummer 111 **6800 WC Arnhem**
Sponsor (in Dutch: verrichter/opdrachtgever)	**Rijnstate Hospital**
Subsidising party	**Rijnstate Hospital**
Independent expert (s)	**Prof. dr. Eric J. Hazebroek**
Laboratory sites <*if applicable*>	**N/A**
Pharmacy <*if applicable*>	**N/A**

PROTOCOL SIGNATURE SHEET

Name	**Signature**	**Date**
Head of Department:	**Drs. Claudia de Swart, Manager Zorg Rijnstate Clinics**	
[Coordinating Investigator/Project leader/Principal Investigator]:	**Dr. Job van Susante, Orthopaedic Surgeon.**	

TABLE OF CONTENTS

LIST OF ABBREVIATIONS AND RELEVANT DEFINITIONS

ABR	**General Assessment and Registration form (ABR form), the application form that is required for submission to the accredited Ethics Committee; in Dutch: Algemeen Beoordelings- en Registratieformulier (ABR-formulier)**
AE	**Adverse Event**
AR	**Adverse Reaction**
ASA	**American Society of Anesthesiologists**
AVG	**Algemeen Verordening Gegevensbescherming**
BMD	**Bone Mineral Density**
BMI	**Body Mass Index**
CA	**Competent Authority**
CCMO	**Central Committee on Research Involving Human Subjects; in Dutch: Centrale Commissie Mensgebonden Onderzoek**
CT	**Computed Tomography**
CV	**Curriculum Vitae**
DSMB	**Data Safety Monitoring Board**
EU	**European Union**
EudraCT	**European drug regulatory affairs Clinical Trials**
GDPR	**General Data Protection Regulation; in Dutch: Algemene Verordening Gegevensbescherming (AVG)**
HU	**Hounsfield Units**
IB	**Investigator's Brochure**
IC	**Informed Consent**
METC	**Medical research ethics committee (MREC); in Dutch: medisch-ethische toetsingscommissie (METC)**
mSv	**Milliesievert**

NCS	**Netherlands Commision for Radiation Dosimetry, in Dutch: Nederlandse Commissie voor Stralingdosimetrie**
PIF	**Patient Information Folder**
PLIF	**Posterior Lumbar Interbody Fusion**
ROI	**Region Of Interest**
(S)AE	**(Serious) Adverse Event**
SOI	**Slide Of Interest**
STZ	**Samenwerkende Topklinische Ziekenhuizen**
SUSAR	**Suspected Unexpected Serious Adverse Reaction**
TLIF	**Transforaminal Lumbar Interbody Fusion**
UAVG	**Dutch Act on Implementation of the General Data Protection Regulation; in Dutch: Uitvoeringswet AVG**
WMO	**Medical Research Involving Human Subjects Act; in Dutch: Wet Medisch-wetenschappelijk Onderzoek met Mensen**
3D	**Three dimensional**

SUMMARY

Background: Lumbar spinal fusion is a surgical procedure that is widely being used to treat spinal pathology. The ultimate goal of this surgical procedure is to achieve bony fusion between two adjacent vertebrae throughout the disc space behind an interbody cage. To date there is a lack of knowledge about the biological process of intercorporal bone graft remodelling towards successful lumbar spine fusion and its association with the development of back and/or leg pain. There is also no quantitative and objective tool available to help determine whether solid fusion has occurred or is in development. Consecutive Hounsfield Unit (HU) measurements may act as a valuable proxy measure for bone graft remodelling and assist in predicting fusion or non-fusion. Results of a recent feasibility study have shown that it was feasible to establish the HU values of the grafted region of interest on consecutive CT-slices using a standardized measurement protocol with excellent intraobserver reliability. However, this study was conducted using available one-year and two-year CT-data from nine participants only. This limited insight into the development of HU values over time and thus the process of bone graft remodelling in the first year after surgery.

Aim and objectives: The main aim of this study is to further the knowledge gained during a recent feasibility study by exploring the use of HU measurements as a quantitative and reliable tool to assess intercorporal bone graft remodelling towards lumbar interbody fusion. Specific objectives of this study are:

1) to explore how the participants' intercorporal bone grafts HU develop over time in the first two years after fusion surgery.

2) to explore the interobserver reliability of the HU measurements.

3) to explore if the participants' upward, downward or no trend in HU values correlate with trends of scores on a commonly used interbody fusion classification and the degree of back and leg pain.

Method: This is an exploratory prospective cohort study using 30 patients between the ages of 45 and 80 with a symptomatic spondylolisthesis (lytic/degenerative/iatrogenic) requiring single-level lumbar interbody fusion (PLIF/TLIF). Participants will be asked to undergo 4 low-dose postoperative CT-scans of the fusion segment over a two year period.

Intervention (if applicable): N/A.

Main study parameters/endpoints: The main outcome of interest will be the participants' individual and group (mean, SD) Hounsfield Unit values of their intercorporal bone graft(s) as calculated from their (four) CT-scans. We will use the standardized HU measurement protocol developed during a feasibility study. The HU will be determined independently by three observers. Secondary outcomes include the Oswestry Low Back Pain Disability Questionnaire (ODI), Short Form-36 (RAND-36), Visual Analogue Scale (VAS) for back and leg pain and the intercorporal fusion result criteria by Brantigan et al.

Nature and extent of the burden and risks associated with participation, benefit and group relatedness: In this study, participants will be asked to undergo four low-dose CT-scans of their instrumented segment over a two year period during their regular care hospital visits. By taking several measures, the patient's effective dose of radiation exposure during the study will be around 7.2 mSV compared to the 3.0 mSv during regular care. As such, compared to regular care, participants will be exposed to a slightly higher dose of radiation by participating in this study.

1. INTRODUCTION AND RATIONALE

Lumbar spinal fusion is a surgical procedure that is widely being used to treat spinal deformities, spondylolisthesis, spondylolysis, spinal instability, and degenerative disc disease [1]. To date, posterior lumbar interbody fusion (PLIF) and transforaminal lumbar interbody fusion (TLIF) are the most widely used techniques [2]. Consensus regarding a superior technique is lacking [3]. During both these surgical techniques the orthopaedic surgeon uses a dorsal approach to remove the intervertebral disc, inserts an intervertebral cage for stability purpose when deemed appropriate, and impacts autologous decompressive bone behind the cage [2]. Over time, this non-vital bone graft can remodel towards new vital bone and subsequently creates a sustainable fusion between two adjacent lumbar vertebral bodies. However, in case of resorption of the bone graft or insufficient bone remodelling, solid bridging of bone may fail to develop and this may result in a pseudarthrosis or non-union. These clinically important complications appear in 5% to 35% of patients treated with spinal fusion and may in turn lead to pain and a decrease in functional status [4]. When bone graft remodelling fails and solid fusion does not occur, subsequent revision surgery for symptomatic pseudarthrosis is often needed. This occurs in up to 24% of patients treated with a fusion [5]. The ultimate goal of a PLIF/TLIF procedure is to achieve bony fusion between two adjacent vertebrae throughout the disc space behind the cage. In order to monitor and evaluate bony fusion, radiographic evaluation using conventional radiographs or CT-scans are commonly used [6-9]. An orthopeadic surgeon can use several existing scoring criteria (e.g. [10-12]) to judge and quantify the degree of bone remodelling and solid bony bridging based on these radiographs. However, these scoring criteria are rather subjective and research has shown that the inter-observer agreement of these scoring criteria is relatively low [6, 11]. The problem is that, to date, there is no quantitative and objective tool available to quantify the bone remodelling process and to judge whether vertebrae have fused or not. In fact, there is an overall dearth of knowledge about the biological process of ongoing spinal fusion and its association with the development of back and/or leg pain.

Hounsfield Units (HU) correlate with bone mineral density (BMD) values and are already used to determine bone quality on CT-imaging [13-18]. However, BMD values are generated using two-dimensional dual-energy X-ray absorptiometry (DEXA) scans which are hindered by overprojection from the iliac crest. This prevents the disc space from being properly scanned. As such, CT-based HU measurements in the interbody graft can be considered as a more suitable proxy measure for the biological remodelling process after spinal fusion. To quantify changes of the grafted disc space over time, repeated CT scans are necessary from early after surgery to at least two years after surgery. The four CT-scans taken during this timeframe will provide the necessary radiological imagery to measure the bone grafts' HU and adequately capture the participants' HU trajectories, thereby elucidating the process of bone remodelling and monitoring the quality and progression of ongoing interbody fusion [10, 11]. For example, patients who clearly show bone remodelling towards fusion (increasing trajectory of HU values) may be monitored less frequently after surgery. This may potentially decrease patient burden (number of hospital visits, travel expenses, radiation exposure because of less radiographs needed) and decrease expenses for health care in general. Conversely, patients who show stationary or decreasing trajectories of HU values combined with lasting complaints of back and/or leg pain, may be followed-up more regularly in order to monitor the development of potential complications (such as pseudarthrosis or non-union) and assist in decision-making regarding the need for re-operation.

Because the use of HU measurements as a means to evaluate bone graft formation after lumbar interbody fusion surgery is scarce, we explored whether it was feasible to assess intercorporal bone graft remodelling by determining CT-based values of HU after lumbar spondylodesis (see Figure 1), and to explore trends in the individual changes in HU over time (see Figure 2) [19]. The research study proposed in this protocol will build upon the results of this study in an effort to further the state of the art in this important field of orthopaedics.

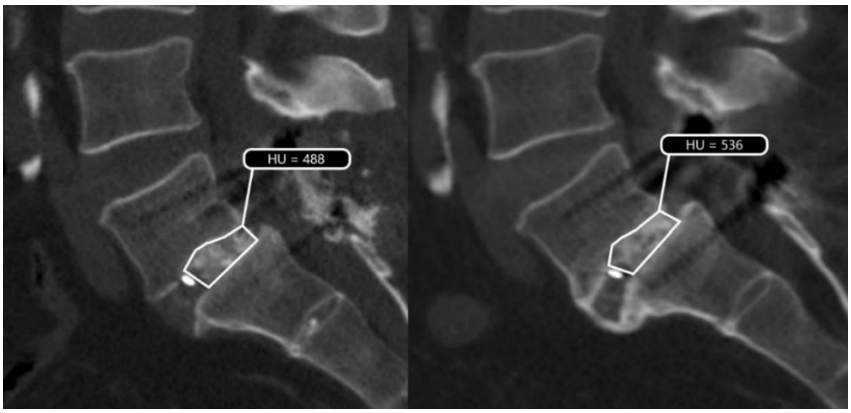


Figure 1 An example of the free-hand drawn regions of interest (ROI) including intercorporal bone graft at one (left) and two (right) years after surgery. The cage markers, which acted as reference points beyond which the ROI was demarcated (posteriorly), are clearly visible on both scans. In this example HU increased from 488 HU to 536 HU over time.

To date only two feasibility studies with relatively small sample sizes have reported on the value of HU measurements to evaluate bone graft remodelling after lumbar interbody fusion surgery. In one previous cross-sectional study [20] published almost 18 years ago, HU measurements were only performed once in the first year after spinal fusion surgery. As such, no information with regards to the evolution of bone graft HU over time after fusion surgery were obtained. This study prompted us to perform a retrospective feasibility study [19] during which we i) explored whether it was feasible to quantify intercorporal bone graft remodelling over time by determining CT-based values of HU after lumbar spondylodesis, and ii) to explore trends in the individual changes in HU over time in the second year after fusion surgery as a proxy measure of the bone graft remodelling process towards intercorporal fusion or non-fusion. The results of this study showed that the HU measurement procedure developed for the study had excellent intraobserver reliability. The results also suggested that prospective follow-up of CT-based HU measurements could potentially be used as a way to judge whether the patients' bone remodelling process is developing towards successful fusion or non-fusion (see Figure 2). However, limitations of this study included a small sample (n = 9), the absence of postoperative CT-images made during the first weeks after surgery and the absence of information about the participants' postoperative back and leg pain. This limited insight into the progression of pain and the process of bone graft remodelling, over time in the first year after surgery. To overcome these limitations we want to conduct a prospective study using a larger sample (n = 30) and incorporate CT-scanning in the first week after surgery, and again after 6, 12 and 24 months.

This method is also well suited to explore the interobserver reliability of our measurement procedure.

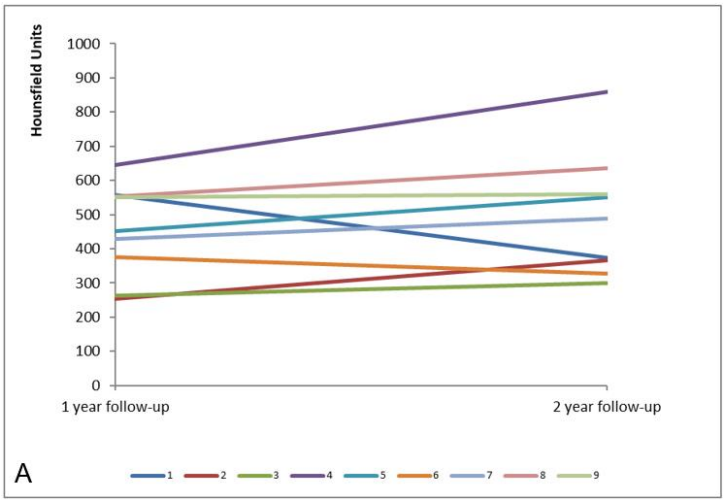


Figure 2 Changes in bone graft HU over time. The change in HU from one- to two-years postoperative. Each line represents a unique patient. Source:[19]

2. OBJECTIVES

This study has three specific objectives:

1) to explore how the participants' intercorporal bone grafts HU develop over time in the first two years after fusion surgery.

2) to explore the interobserver reliability of the HU measurements.

3) to explore if the participants' upward, downward or no trend in HU values correlate with trends of scores on a commonly used interbody fusion classification and the degree of back and/or leg pain.

3. STUDY DESIGN

This is a single-center prospective exploratory study. During this study a convenience sample of participants, who have undergone lumbar spinal fusion in Rijnstate Hospital and who have agreed to participate in the study, will have (four) CT-scans of the lumbar spine taken in the first two years after surgery: one in the first week after surgery and one again after 6, 12 and 24 months. Clinical outcome questionnaires will also be obtained during those set times.

4. STUDY POPULATION

4.1 Population (base)

We will recruit 30 patients with a symptomatic spondylolisthesis (lytic/degenerative/iatrogenic) who have an indication for single level lumbar interbody fusion (PLIF/TLIF).

4.2 Inclusion criteria

Patients are only eligible for participation if they i) were non-responsive to non-operative treatment in the six months prior to study enrolment, ii) have fusion indicated for only one segment in the L1 to S1/ilium region and iii) are between the age of 45 and 80.

4.3 Exclusion criteria

Patients will be excluded from participation if they i) will receive *revision* spine surgery, ii) do not want to provide informed consent or when iii) pregnant or expecting to be pregnant within in the next two years.

4.4 Sample size calculation

To our knowledge, no previous studies have evaluated differences in HU values of intercorporal bone grafts over time. Because of the lack of data, establishing the sample size needed is challenging. However, the results of our recently conducted feasibility study (n = 9) [19] have shown that participants had a mean HU value of around 448 (SD ± 145) after one year, and a mean HU value of around 483 (SD ± 142) after two years, respectively. The expected mean of the paired differences was approximately 35 and the expected standard deviation of the paired differences was approximately 64. Although it is not the aim of this study to calculate whether there are statistically significant differences in the participants' HU values over time (but rather to evaluate if and how HU values change over time postoperatively) we chose to perform a sample size calculation (for comparing

paired differences) as to prevent inviting too little or too many participants for the CT-scans. To achieve a power of 80% and a level of significance of 5% (two-sided) for detecting a mean of the differences of 35 between pairs, 29 participants would be needed (http://statulator.com/SampleSize/ss2PM.html). To compensate for possible participant drop-out (which in our experience is minimal in these types of studies) we aim to recruit 30 participants.

5. TREATMENT OF SUBJECTS

N/A

6. INVESTIGATIONAL PRODUCT

N/A

7. NON-INVESTIGATIONAL PRODUCT

N/A

8. METHODS

8.1 Study parameters/endpoints

8.1.1 Main study parameter/endpoint

The main outcome of interest will be the participants' individual and group (mean, SD) Hounsfield Unit values of their intercorporal bone graft(s) as calculated from their (four) CT-scans. We will use the standardized HU measurement protocol developed during a feasibility study. The HU will be assessed independently by three observers.

8.1.2 Secondary study parameter/endpoint

Secondary outcomes include the Oswestry Low Back Pain Disability Questionnaire (ODI), Research and Development-36 (RAND-36), Visual Analogue Scale (VAS) for back and leg pain and the intercorporal fusion result criteria by Brantigan et al. (figure 3). The questionnaires can be found in the Appendix section of this protocol.

8.2 Randomisation, blinding and treatment allocation

N/A

8.3 Study procedures

After surgery, participants will undergo a total of four postoperative CT-scans of the lumbar spine: one in the first week after surgery and one again after 6, 12 and 24 months.

8.4 Withdrawal of individual subjects

Participants can leave the study at any time for any reason if they wish to do so without any consequences. The investigator can decide to withdraw a participant from the study for any medical reasons.

8.4.1 Specific criteria for withdrawal

Participants who have received a too low amount of intervertebral bone graft that precludes proper assessment of HU (as judged by a radiologist) will be withdrawn from the study after the first study CT-scan. These participants will subsequently be followed-up as per regular care.

8.5 Replacement of individual subjects after withdrawal

N/A

8.6 Follow-up of subjects withdrawn from treatment

N/A

8.7 Premature termination of the study

The study will be terminated if no more than 15 participants have provided their Informed Consent (IC) within nine months after the start of the study. All included participants will be notified in case of premature termination of the study.

9. SAFETY REPORTING

9.1 Temporary halt for reasons of subject safety

In accordance with section 10, subsection 4, of the WMO, the sponsor will suspend the study if there is sufficient ground that continuation of the study will jeopardise subject health or safety. The sponsor will notify the accredited METC without undue delay of a temporary halt including the reason for such an action. The study will be suspended pending a further positive decision by the accredited METC. The investigator will take care that all subjects are kept informed.

9.2 AEs, SAEs and SUSARs

All serious or life-threatening SAEs will be directly reported to the principal investigator and this will also be presented to the reviewing adjudication committee within the set dates of 7 days. Non-life-threatening SAEs will be presented to the reviewing committee within 15 days after notification.

9.3 Annual safety report

N/A

9.4 Follow-up of adverse events

N/A

9.5 [Data Safety Monitoring Board (DSMB) / Safety Committee]

N/A

10. STATISTICAL ANALYSIS

The participant characteristics, spinal fusion surgery-related data and secondary outcomes will be summarized in terms of frequencies (percentages of total), medians (interquartile range) or means (standard deviations).

The HU measurement values will be presented descriptively in terms of individual values and group means (standard deviations). We will also plot the HU trajectories using line graphs to illustrate how the HU of individual participants have developed over time.

To evaluate the interobserver reliability of the HU measurements we will calculate Intraclass Correlation Coefficients (95% confidence interval) between the three observers using the single-rating, absolute agreement, two-way random-effects model.

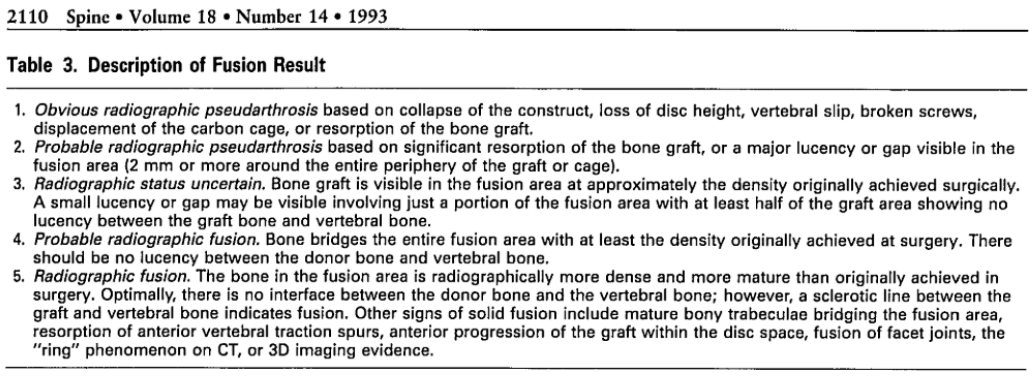
To calculate the association between the participants' upward, downward or no trend in HU values, the trend in scores on the interbody fusion classification by Brantigan and pain scores we will calculate Chi-square tests for trend.

10.1 Primary study parameter(s)

The main outcome of interest will be the participants' individual and group (mean, SD) Hounsfield Unit values of their intercorporal bone graft(s) as calculated from their (four) CT-scans. We will use the standardized HU measurement protocol developed during a feasibility study. The HU will be determined independently by three observers.

10.2 Other study parameters

The secondary outcomes include the Oswestry Low Back Pain Disability Questionnaire (ODI), Research and Development-36 (RAND-36), Visual Analogue Scale (VAS) for back and leg pain and the intercorporal fusion result criteria by Brantigan et al. [10] (see Figure 3). The baseline questionnaires are sent to the patient within 2 days after enrollment and follow-up questionnaires are sent to the patients within 2 days upon completion of the follow-up CT-scan.



2110 Spine • Volume 18 • Number 14 • 1993

Table 3. Description of Fusion Result

1. *Obvious radiographic pseudarthrosis* based on collapse of the construct, loss of disc height, vertebral slip, broken screws, displacement of the carbon cage, or resorption of the bone graft.
2. *Probable radiographic pseudarthrosis* based on significant resorption of the bone graft, or a major lucency or gap visible in the fusion area (2 mm or more around the entire periphery of the graft or cage).
3. *Radiographic status uncertain.* Bone graft is visible in the fusion area at approximately the density originally achieved surgically. A small lucency or gap may be visible involving just a portion of the fusion area with at least half of the graft area showing no lucency between the graft bone and vertebral bone.
4. *Probable radiographic fusion.* Bone bridges the entire fusion area with at least the density originally achieved at surgery. There should be no lucency between the donor bone and vertebral bone.
5. *Radiographic fusion.* The bone in the fusion area is radiographically more dense and more mature than originally achieved in surgery. Optimally, there is no interface between the donor bone and the vertebral bone; however, a sclerotic line between the graft and vertebral bone indicates fusion. Other signs of solid fusion include mature bony trabeculae bridging the fusion area, resorption of anterior vertebral traction spurs, anterior progression of the graft within the disc space, fusion of facet joints, the "ring" phenomenon on CT, or 3D imaging evidence.

Figure 3 The 5-point intercorporal fusion criteria by Brantigan et al.

10.3 Interim analysis (if applicable)

N/A

11. ETHICAL CONSIDERATIONS

11.1 Regulation statement

This study will be conducted according to the principles of the Declaration of Helsinki (as adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964, and amended by the 64th WMA General Assembly, October 2013, Fortaleze, Brazil) and in accordance with the Dutch Medical Research Involving Human Subjects Act (WMO).

11.2 Recruitment and consent

First, potential eligible participants will be approached by their treating orthopedic surgeon who will introduce the study and thereafter handing or sending them a Patient Information Form (PIF) which includes the Informed Consent Form (IC, see Appendix C). One week after handing or sending the PIF/IC, the coordinating researcher will contact the patient by phone to ask whether the patient has any questions about the study, and whether he/she is willing to participate. Participants willing to participate will be asked to sign and return the IC to the coordinating researcher.

11.3 Objection by minors or incapacitated subjects (if applicable)

N/A

11.4 Benefits and risks assessment, group relatedness

Participating in this study has no benefits for participants.

Participants will be asked to undergo four low-dose CT-scans of the instrumented segment over a two year period. During standard care, fusion patients undergo three conventional lumbar radiographs (after 6 weeks, 3 months, and 1 year) and one CT-scan (after 1 year). In our hospital, the effective median exposure doses of standard lumbar radiographs and CT-scans are 0.2 mSv and 2.4 mSv, respectively. This exposes each patient to a total radiation dose of (3 x 0.2 + 1 x 2.4) = 3.0 mSv in one year. Without taking any additional measures, four ‘study’ CT-scans would expose the participants to a total radiation dose of (4 x 2.4 =) 9.6 mSv over a two year period. To mitigate this increased radiation risk, and to lower the participants’ radiation exposure during the study, we will:

1) focus the CT-scan of the lumbar region on the instrumented segment only (2 instead of the regular 6-7 vertebral bodies). This measure will reduce the radiation dose by 0.6 mSv

(and to a total of 1.8 mSv per CT-scan), and hence reduce the overall CT-based radiation dose by (4 x 0.6 =) 2.4 mSv.

2) replace the conventional lumbar radiographs by the study CT-scans. This measure will prevent participants from also receiving a standard radiation dose of 3 x 0.2 = 0.6 mSv from the radiographs.

By taking the above two measures, the patient's effective dose of radiation exposure during the study will be around 7.2 mSV compared to the 3.0 mSv during regular care. As such, compared to regular care, participants will be exposed to a slightly higher dose of radiation by participating in this study. It is also of note that we will only recruit patients over the age of 45. In this age group the lifetime risk of radiation induced carcinogenesis is known to decline rapidly [21, 22].

Considering the above, and applying the risk classification as proposed by the Dutch Commission for Radiation Dosimetry (NCS) [23] the additional radiation risk is moderate ("matig risico", category IIb). We believe that the benefits, of gaining insight in how patients' intercorporal bone grafts HU develop over time in the first two years after fusion surgery, and if the patients' upward, downward or no trend in HU values correlate with trends of scores on a commonly used interbody fusion classification and the degree of back and leg pain, outweighs this risk.

11.5 Compensation for injury

This research falls under the scope of the WMO. Rijnstate has a liability insurance which is in accordance with article 7 of the WMO. The sponsor (also) has an insurance which is in accordance with the legal requirements in the Netherlands (Article 7 of the WMO). This insurance provides cover for the unlikely damage to research subjects through injury or death caused by the study.

11.6 Incentives (if applicable)

N/A

12. ADMINISTRATIVE ASPECTS, MONITORING AND PUBLICATION

12.1 Handling and storage of data and documents

All data handling and storage will comply with the EU General Data Protection Regulation and the Dutch Act on Implementation of the General Data Protection Regulation (Dutch: Uitvoeringswet AVG). All data collected during this study will be managed according to the FAIR principles in order to enhance and improve Findability, Accessibility, Interoperability and Reuse of research data. All research and patient related data will be stored in Research Manager, a cloud based data storage system with ISO 27001: 2013 certification as well as Good Clinical Practice (GCP) and NEN7510 compliancy.

The coordinating investigator/project leader (JFHR) will collect the patient source data from the electronic patient records. These data comprise the participant's hospital identification number, their patient characteristics and spinal fusion surgery-related data. All patient data will be handled confidentially. Each subject will be given an identification code and only the investigators involved in this study will have access to the subject identification code list which can be used to link the data to the patient. After full data collection data will be transferred to an IBM Statistical Package for the Social Sciences (SPSS, version 25.0; IBM Corp, Armonk, NY) spreadsheet. In this spreadsheet the participants data will be non-identifiable / anonymous. The code is based on consecutive numbers. The data files will be securely saved in a research folder on the hospital's computer mainframe. All data collected during this study will be kept under secure conditions at Rijnstate Hospital for 15 years after the research has ended and then it will be destroyed. Any information collected will be treated as confidential and used only in this study unless otherwise specified. All source data relating to consented study participants will be stored and processed in line with Rijnstate Hospital

requirements. All source data held in paper form (Informed Consents) will be scanned and securely stored as soon as possible after the participants has signed it. Paper copies will be stored in the secured research lockable cabinet at the department of Orthopaedics.

12.2 Monitoring and Quality Assurance

Monitoring of the study will take place during the total study duration according to guidelines set out by the Samenwerkende Topklinische Ziekenhuizen (STZ) and as described in Standard Operating Procedure 'STZ SOP VC12 Monitoringplan' (STZ version 21-02-2019; Rijnstate version 8-5-2019). Monitoring will be performed by Rijnstate's own local Research Ethics Office.

12.3 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.

12.4 Annual progress report

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

12.5 Temporary halt and (prematurely) end of study report

The investigator/sponsor 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 patient's last visit. The sponsor will notify the METC immediately of a temporary halt of the study, including the reason of such an action.

In case the study is ended prematurely, the sponsor will notify the accredited METC within 15 days, including the reasons for the premature termination. Within one year after the end of the study, the investigator/sponsor will submit a final study report with the results of the study, including any publications/abstracts of the study, to the credited METC.

12.6 Public disclosure and publication policy

This study will be prospectively registered in a public trial registry before the first patient is recruited. All data will be the property of Rijnstate. Publication will be the responsibility of the coordinating and principal investigators. It is planned to publish the results of this study in a peer-reviewed journal and to present results at national and international meetings. It will not be possible to identify any individuals from any publication or presentation.

13. STRUCTURED RISK ANALYSIS

In this study, participants will be asked to undergo four low-dose CT-scans of their instrumented segment over a two year period during their regular care hospital visits. By taking several measures, the patient's effective dose of radiation exposure during the study will be around 7.2 mSV compared to the 3.0 mSv during regular care. As such, compared to regular care, participants will be exposed to a slightly higher dose (4.2 mSv additional radiation) of radiation by participating in this study. According to the Dutch Radiation Committee for Radiation Dosimetry, this additional radiation poses a moderate risk ("matig risico") to participants [23].

14. REFERENCES

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