Clinical Investigation Plan

Observational clinical study with Surgical Navigation to plan, position and check instrument placement for spine surgery interventions

Security Classification: **Confidential**

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APPROVAL PHILIPS

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REVISION HISTORY

Date	Rev.	Author	Changes/Comments
2015 May 26	1.0	[redacted]	Initial version
2016 June 30	2.0	[redacted]	Changes: • Name of investigational device Light2C replaced with Surgical Navigation • [redacted]Optical marker supplier company has been changed from [redacted] • Human cadaver study section updated with additional human cadaver experiments • Risk of Surgical Navigation and unanticipated adverse events have been updated after latest risk assessment and implementation of mitigations • Inclusion criteria change: age decreased from 18 to 16 years to allow also scoliotic patients in the study. • Sample size has been updated to 240 screws and anticipated number of patients has been changed to 15 to 25 patients due to the expected inclusion of scoliotic patients. • Typographical error have been corrected
2016 July 08	3.0	[redacted]	• Removed sterile drapes from device description. Sterile drapes for detector compatible with the Allura and surgical navigation (Microtek Medical, Zutphen, The Netherlands) is a separate disposable that can be used in combination with the Allura system, like common used drapes. CE-labeled drapes are used in the study and they are not part of the surgical navigation device. • Added clarification that optical markers will be supplied via Philips Healthcare during the study.

Date	Rev.	Author	Changes/Comments
2016 July 14	4.0	[redacted]	• Added a Data Monitoring Committee (DMC/DSMB) since subject with age of 16 years and older are included in the study. DMC will review adverse events and serious adverse events and will provide recommendations of continuation of the study at multiple moments.
2016 Aug 15	5.0	[redacted]	• Clarified that final risk assessment has been performed and included conclusion of final risk assessment on request of the MPA
2016 Sep 16	6.0	[redacted]	• Added clarification of “Entry point” • Explanation has been added to why an observation, non-randomized study design has been chosen. • Reference to Light2C has been replaced with Surgical Navigation in Figure 5 and 7 • XperGuide clinical experience section has been updated with reference for general complication of vertebral augmentation and post-market safety data. • Anticipated adverse device effects section has been updated with likely incidence, mitigation or treatment. • Retention period has been updated at the investigational site to address only national requirements of Sweden • Amendment section had been updated with approval requirements • Adverse event definitions and reporting has been updated according to MEDDEV 2.7/3 rev 3 • Definitions for entry point and placement has been added to the section abbreviations
2016 Oct 04	7.0	[redacted]	• Removal of Section 12.1 since patients unable to read, understand and sign for themselves are excluded from study participation as per Informed Consent.

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Three medical devices will be used in this observational clinical study with Surgical Navigation to perform image-guided spine surgery navigation (see Table 1 and Figure 1).

Table 1: Medical devices involved in this clinical study with Surgical Navigation to perform image-guided spine surgery navigation

#	Device description	Manufacture	Investigational/ CE labeled during the study
1	Angiographic X-ray system Allura FD20	Philips Medical Systems, *a Philips Healthcare company,* Best, The Netherlands	CE label
2	Surgical Navigation application	Philips Medical Systems, *a Philips Healthcare company,* Best, The Netherlands	Investigational device
3	Fiducials/optical markers (disposal)	[redacted] (item Optical Marker or similar) Supplied via Philips Healthcare during the trial	CE label

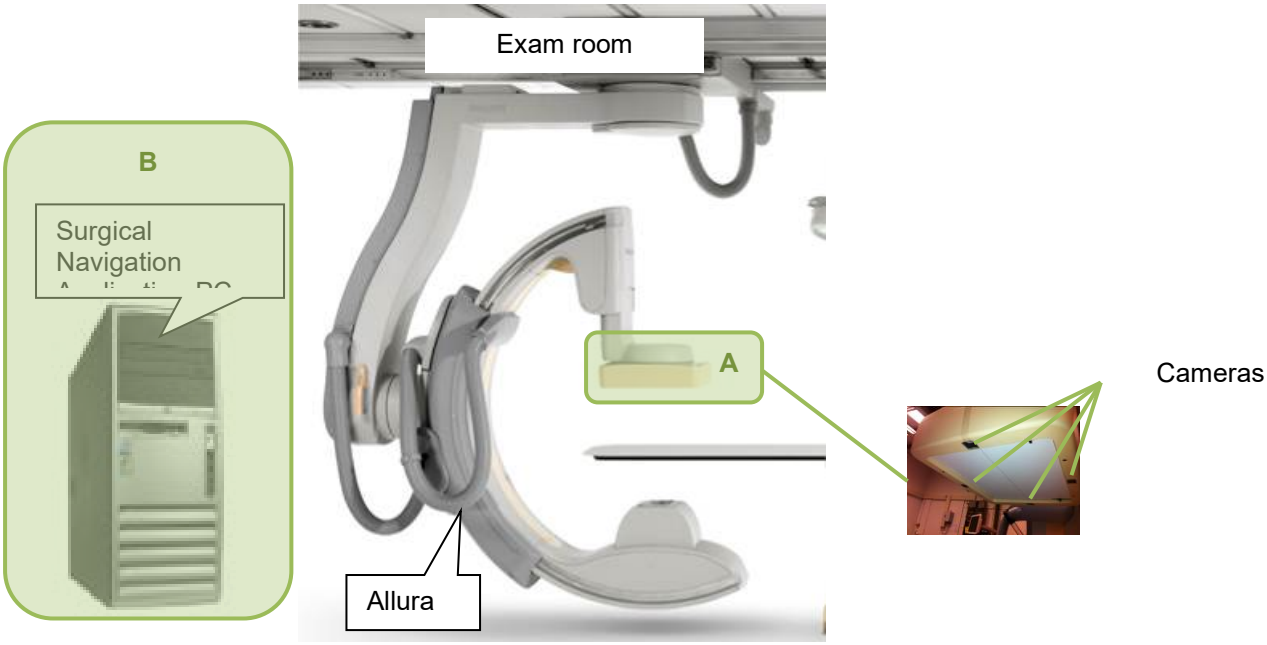

Figure 1: Graphic overview of the Surgical Navigation applications and angiographic X-ray system Allura used in this study.

A=detector frame of the C-arm with four small optical cameras, B= Surgical Navigation application software running on a PC.

Surgical Navigation is an intra-operative image-guidance software application used during surgical and interventional therapy. Surgical Navigation is intended to be used in combination with a Philips interventional X-ray system Allura with ORT table.

Angiographic X-ray system Allura FD20

Angiographic X-ray system Allura FD20 (further called Allura in this study plan) will contain four small optical cameras in the detector frame of the C-arm. On each side of the detector one camera is located. The cameras are connected to a PC where the Surgical Navigation application is running.
The optical images and X-ray images (e.g. 2D fluoro, 3D Cone Beam Computed Tomography (CBCT/XperCT/CT-like image)) are acquired with the Allura. Since the cameras are rigidly connected to the detector-suspension frame in the Allura, the relative position between camera and detector can be measured once and does not change. So a position registration before a clinical procedure is not

necessary (the camera-to-detector position & orientation is calibrated by Philips).

Surgical Navigation application

The Surgical Navigation application-software (further called Surgical Navigation in this study plan) is an investigational device and is running on an application PC.

[redacted]

[redacted]

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[redacted]

Figure 2: [redacted]

Figure 4:

Study design

This is a prospectively planned, single arm, single center study designed to estimate the accuracy of the pedicle screw placement using the Surgical Navigation procedure in patients undergoing pedicle screw fixation surgery. Accuracy will be reported by the proportion of pedicles having either grade 0 or 1 according to a slightly adapted Gertzbein[4] classification. The slightly adapted Gertzbein[4] classification for pedicle screw breach is defined as follows:

- grade 0 = breach 0 mm
- grade 1 = lumbar and thoracic < 2 mm, cervical <1 mm breach distance
- grade 2 = lumbar and thoracic 2-4 mm, cervical 1-2 mm breach distance
- grade 3 = lumbar and thoracic > 4 mm, cervical >2 mm breach distance.

The proportion of screws placed according to grade 0-3 will be estimated overall, and by region (e.g., cervical, lumbar, and thoracic).

Objectives

Primary objective:
to estimate the accuracy of pedicle screw placement using Surgical Navigation on post-procedural CBCT:

Screw placement will be evaluated using a slightly adapted Gertzbein4 classification for pedicle screw breach as follows:
grade 0 = breach 0 mm
grade 1 = lumbar and thoracic < 2 mm, cervical <1 mm breach distance
grade 2 = lumbar and thoracic 2-4 mm, cervical 1-2 mm breach distance
grade 3 = lumbar and thoracic > 4 mm, cervical >2 mm breach distance.

Accuracy will be reported by the proportion of pedicles having either grade 0 or 1.

Secondary objective(s):

1) To estimate the procedure time.
2) To estimate the average time to insert a pedicle screw.
3) To estimate the length of hospitalization (LOH)
4) Collect System Usability Scale (SUS) and assess the clinical workflow related to easiness to work,

image quality, real-time image update, preparation of patient tracking, confidence in image guidance, access planning, 3D segmentation, motion compensation, identify unknown potential use errors and evaluate risk controls.

5) To estimate radiation dose (Dose Area Product (DAP) and Air Kerma (AK)) delivered to patient for:
    a. Total procedure
    b. During preparation and acquisition of CBCT for path planning
    c. During screw/instrument placement (using fluoro).
    d. During preparation and acquisition of CBCT for confirmation
    e. Average procedure dose per planned path
6) To estimate the total radiation dose (effective dose) received by operator, if DoseAware Xtend is available.
7) To describe procedure related complications
8) Report all adverse events
9) Report all adverse device effects
10) Report all device deficiencies that could have led to a serious adverse event

Primary and secondary endpoints

The primary endpoint of the study is accuracy.
1) This is measured according to an adapted version of the in literature reported classification method by Gerztbein, so that it includes distance of breaches applicable for cervical region besides the lumbar and thoracic region.

Furthermore, accuracy will also be reported by direction of breach (lateral/medial), and distance between planned path and screw in smallest area of the pedicle (mm) and the distance between screw tip and planned target of screw (mm).

Secondary endpoints are:
Procedure time, time to insert a pedicle screw, Length of hospital Stay, System Usability Score, patient radiation dose (DAP and AK and fluoro time), occupational radiation dose (effective dose), procedure related complications, adverse events, adverse device effects, device deficiencies that could have led to a serious adverse event.

Main inclusion criteria

- Subject will be undergoing a spine surgery with pedicle screw placement
- Subject is 16 years of age or older
- Subject is able to give informed consent

Main exclusion criteria

- Subject participates in a potentially confounding device or drug trial during the course of the study.
- Subject meets an exclusion criteria according to national law (e.g. pregnant woman, breast feeding woman)

No. of subjects

In total 240 screws placement are needed. It is expected that approximately 15 to 25 subjects with pedicle screw surgery are necessary to collect sufficient data for the evaluation of the primary and secondary objectives of this clinical investigation. After the first two subjects have been treated with pedicle screws there will be a delay of at least 1 week until the third and fourth subjects will be undergoing the procedure with Surgical Navigation. After subject one to four have been treated and the DMC/DSMB have been given recommendations of continuation of the study then there is no limit on how many subjects can be treated during one day. Enrollment of subjects will be stopped after approximately 240 screws are placed. This is a common number of screws used in studies showing accuracy of pedicle screw placement in the cervical. The enrollment period is expected to last for 7 months.

Study procedures

Pedicle screw placement

Pedicle screws will be placed using Surgical Navigation image guidance during spine surgery. The specific clinical investigation related steps for this spine surgery are (see also Figure 8):

- Sterile drapes compatible with the Allura and Surgical Navigation with transparent windows are

placed over the detector.
- Several optical markers stickers (4-6 depending on the size of the region of interest) are placed at the back of the patient around the area of interest.
- A 3D CT like image is made (CBCT) of the relevant vertebrae.
- The spine image can be segmented using Surgical Navigation, if desired.
- The optimal path for the screw/instrument is planned in the CBCT volume.
- The optical view of Surgical Navigation is used to align the instrument (e.g. K-wires, screws instrumentation) with the planned path at the entry point. Progression view (view perpendicular to the planned path) using fluoro can be used during insertion of the screw, if desired. With this progression view function, the user can check on an x-ray image the actual placement of the screw at each moment in the procedure.
- The pedicle screws/instrumentation are further inserted in the vertebra using tools according to standard of care.
- Acquisition of a CBCT showing all placed pedicle screws/instrumentation to check the success of the procedure. This CBCT replaces the standard post-operative CT to check the procedure.
  For pedicle screw placement: Like in normal clinical practice, the necessity for revision of a pedicle screws is determined based on 3D information. This CBCT with the pedicle screws will be used to determine the accuracy of pedicle screw placement for the objectives of this study. The physician will indicate the classification according to the classification system (grade 0-3, see section 4.1). This classification can be done post-procedure.
- Time of the total procedure will be measured.
- Patient and occupational dose data will be collected using Surgical Navigation and DoseAware Xtend (if available at the hospital), respectively.

Patients participating in this study are subject to follow-up until hospital discharge to collect the length of hospital stay.

All other things are the same as the current standard of care.

All post-procedural CBCT acquisitions will be evaluated by an independent reviewer (neurosurgeon, orthopedic surgeon or spine surgeon experienced in pedicle screw placements) to determine the accuracy of pedicle screw placement according to the modified Gertzbein grading system (grade 0-3, see section 4.1) and direction (lateral/medial breach).
Furthermore, the distance (mm) between the following two points will be measured:
- The planned path and screw axis at smallest pedicle diameter
- The planned path and at the tip of the screw

The classification by the independent reviewer will be used for the objectives.

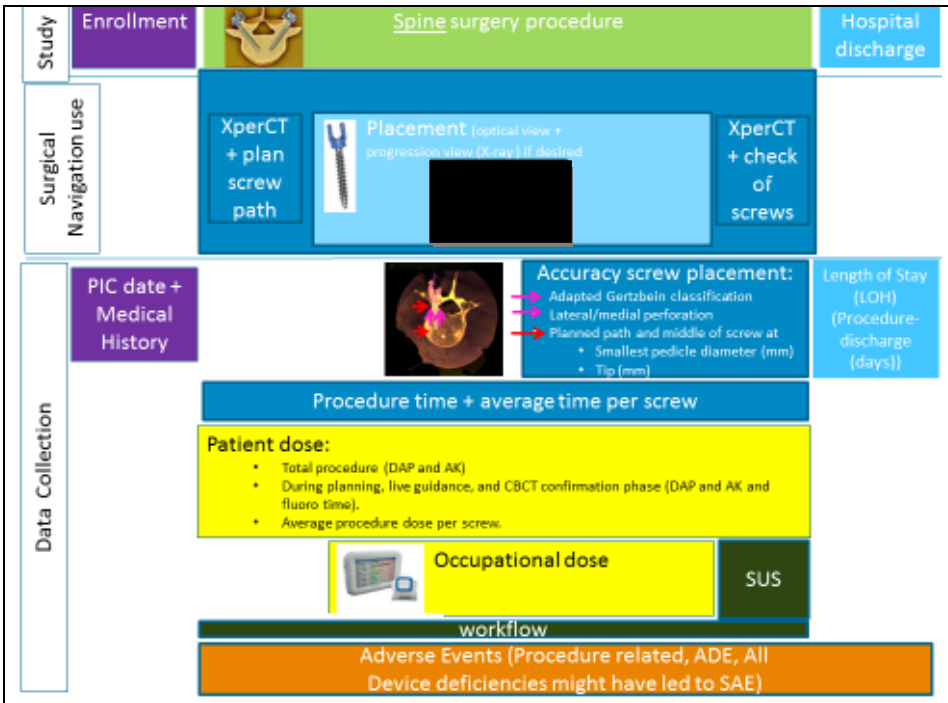

Figure 8: Flowchart for patient undergoing pedicle screw placement

Workflow feedback and usability information

Observations related to the workflow for the spine procedure will be performed by a Philips representative during some of the procedures. Workflow feedback will also be obtained through a short interview with the physician performing the procedure.

At the end of the study the physician(s) performing the procedure will be requested to complete a System Usability Scale (SUS) questionnaire to obtain general information related to the usability of Surgical Navigation related to these spine procedures.

Follow up
The subjects will be followed-up for this study until hospital discharge. After this the patient will be followed up according to standard of care outside the study.
Duration of the study
The total duration of the study is expected to take approximately 1 year

1. DEVICE DESCRIPTION

1.1. Summary description of the investigational device

Three medical devices will be used in this observational clinical study with Surgical Navigation to perform image-guided spine surgery navigation (see Table 1 and Figure 1, duplicated below).

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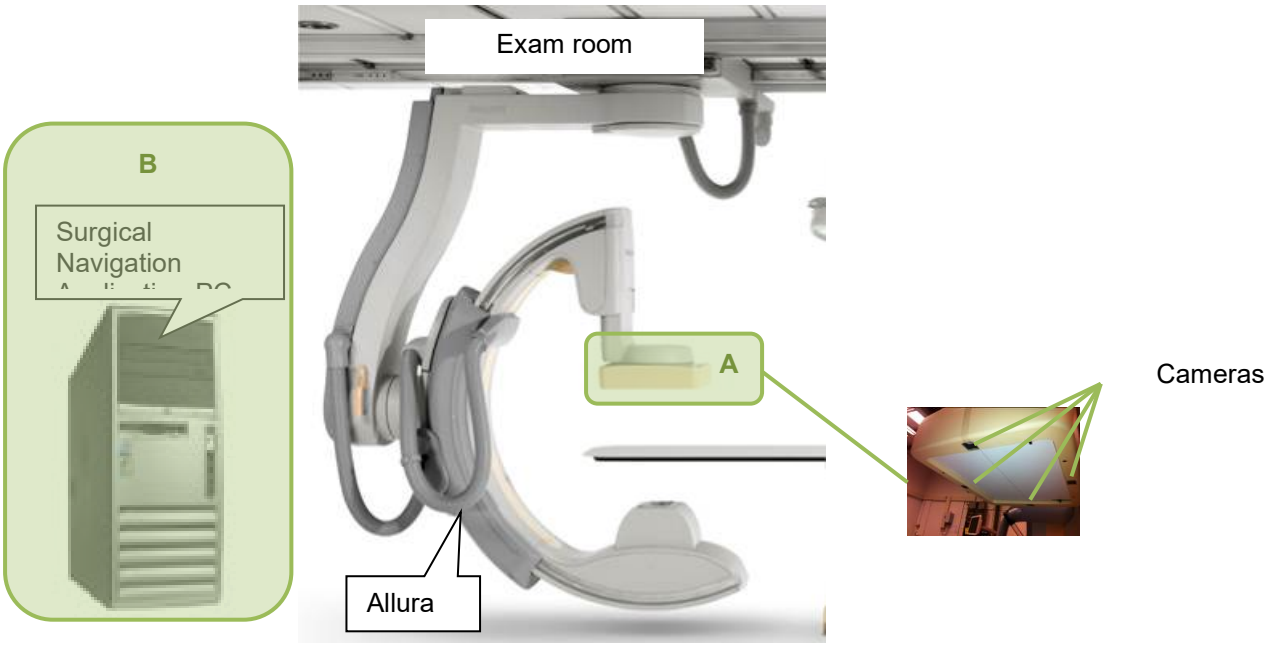

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Surgical Navigation application
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[redacted]

[redacted]

Figure 2: [redacted]

Figure 3: [redacted]

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The manufacturer of the investigational device Surgical Navigation is:
Philips Medical Systems Nederland B.V., a Philips Healthcare company
Veenpluis 4-6
5684 PC Best
The Netherlands

1.2. Intended Purpose

The intended purpose of the investigational device in the proposed clinical investigation is:

Medical purpose
Surgical Navigation is intended to be an intra-operative image-guidance tool used during surgical and interventional therapy. It provides assistance to the performing physician to align an instrument with a virtual path, that is planned on a 3D volume of the anatomy. The virtual path is superimposed with a live video image of the area of interest. It is intended to assist in the treatment of spinal diseases during procedures such as pedicle screw placements and biopsies.

Patient population
Surgical Navigation is suitable for use on patients who have been elected for pedicle screw placement or biopsy

Intended operator profile
The Operator is a physician who is fully skilled and responsible for sound clinical judgment and for applying the best clinical procedure, for example (but not limited to):

- Orthopedic/spine/neuro surgeon
- Skilled radiology technician (or nurse) assisting the physician

To facilitate safe and efficacious operation of the system by a trained healthcare professional, instructions for use are provided as part of the device labelling, as well as a basic training at system handover. The Instruction for Use (IFU) contains safety precautions and handling of the investigational device.

1.3. Necessary training and experience needed to use the investigational device

Adequately trained, qualified, and authorized health care professionals who have understanding of the safety information and emergency procedures as defined by local laws and regulations for radiation workers and staff is needed to use the Surgical Navigation.

1.4. Materials that will be in contact with tissues or body fluids

No materials of the investigational device will be in contact with tissue or body fluids.

1.5. Device Traceability

Traceability of investigational device will be achieved during the study and after the clinical study by the following identification.

Surgical Navigation Device	Identified by:
Software system installation sets	Will be identified by Surgical Navigation software archive ID in combination with unique software revision number

Records shall be kept to document when the device is received, installed or uninstalled at the hospital.

2. JUSTIFICATION FOR THE DESIGN OF THE STUDY

In spine surgery pedicle screws are used for fixation of the vertebrae to stabilize the vertebral column. Conditions where spinal fusion with pedicle screws may be considered include: degenerative disc disease, disc herniations, spinal deformity (scoliosis, kyphosis), spinal stenosis, sciatica, and radiculopathy, spine fractures and trauma, vertebral compression fracture, spine tumors, spondylolisthesis, spondylolysis, and spinal instability.

There is a clear need in spine surgery to place pedicle screws in the right place in the spine with good accuracy to avoid damage to important structures (spinal cord, nerve roots or vertebral arteries).

Thoracic levels (T3-T9) have the narrowest pedicles[1] and have decreased space between the medial border of the pedicle and spinal cord. Studies have estimated that screws placed in this region have a maximum permissible translational/rotational error tolerances ranged from 0.0 mm/0.0° at T5 to 3.8 mm/12.7° at L5 due

to anatomically small pedicle diameters[2]. Screw revision can be difficult and time-consuming (13.8±9.9 min), as the faulty screw track often hinders effective screw repositioning[3]. When considering screw revision time and possible decreases in biomechanical stability, it is important to place the pedicle screws correctly in the first attempt.

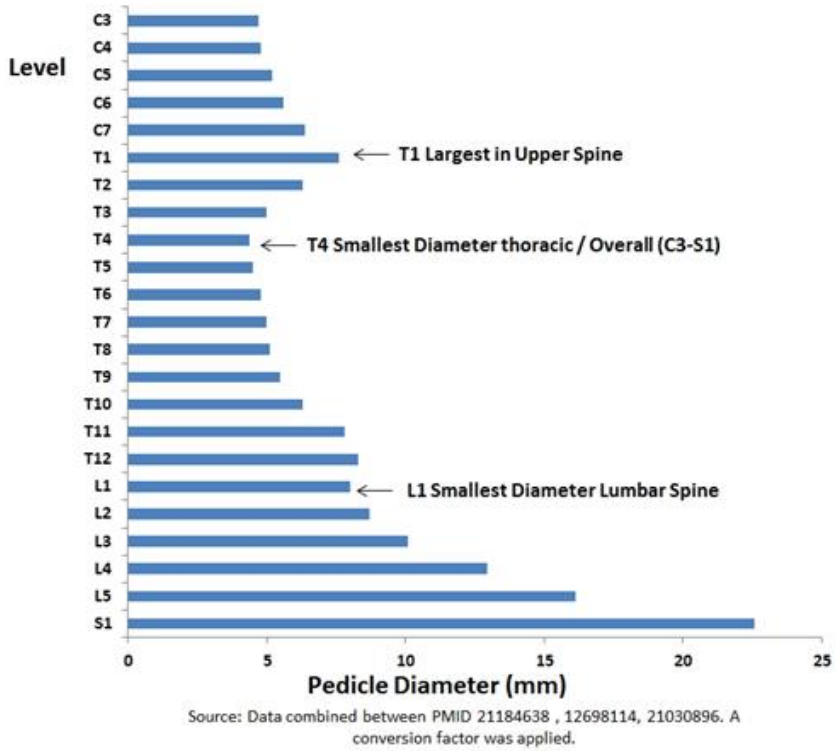

Figure 4: pedicle screw diameter

Image-guided spine surgery

The vast majority of pedicle screw placements in spine are performed using free-hand technique with or without use of 2D fluoro-guidance to place pedicle screws. Next to these conventional methods, image-guided navigation has become available as another technique to improve the accuracy of pedicle screw placement. Navigation systems are using different types of image data, i.e. either pre-operatively acquired CT images or intra-operatively acquired fluoroscopy images, intraoperative CBCT (e.g. O-arm (Medtronic)) or intra-operative acquired CT (e.g. AIRO iCT (Brainlab)). Intra-operative registration relies on the identification of anatomical landmarks, surface contours or pre-operatively implanted fiducial markers.

[redacted]

The accuracy of pedicle screw placements and the misplacements have been reported in the past using the conventional methods. Misplacement has been reported up to 30% in the lumbar and 55% in the thoracic spine [4,5,6]. Image-guided approaches have been investigated and partially implemented into clinical routine in virtually any field of spine surgery. However, the data available is mostly limited to small clinical series, case reports or retrospective studies. Only a couple of Randomized Controlled Trials (RCT) and a couple of meta-analysis have been retrieved concerning image-guided approaches for pedicle screw insertion. Overall, image-guided navigation for pedicle screw placement results in a higher pedicle screw placement accuracy than with conventional methods.

Results of the randomized trials and meta-analysis are summarized below and Table 2, ranging from 81%-100% accuracy for image-guided navigated and 68%-94% with conventional methods.

Tjardes[7] made an overview on the current knowledge concerning the technical capabilities of image-guided approaches. He selected 276 relevant papers in the analysis. Since the advent of high-speed computer workstations allowing the integration of 3D image processing and real time tracking of smart tools the feasibility of image-guided approaches of virtually any application in spine surgery has been proven. Clinical data suggest that image-guided techniques assist in placing pedicle screws accurately; however the thoracic spine remains a critical area due to the small diameters of the pedicle.
Laine describes that in the randomized study the pedicle perforation rate was 13.4% in the conventional group and 4.6% in the computer-assisted group (P =0.006) for thoracolumbar and lumbosacral pedicle screws. Pedicle perforations of more than 4 mm were found in 1.4% (4/277) of the screw insertions in the conventional group, and none in the computer-assisted group[8].
In another randomized study, Rajasekaran[9] reported 54 (23%) pedicle breaches in the thoracic region in the non-navigation group as compared to only 5 (2%) in the navigation group (P < 0.001). Thirty-eight screws (16%) in the non-navigation group had penetrated the anterior or lateral cortex compared to 2 screws (0.8%) in the navigation group.
A meta-analysis by Kosmopoulos and Schizas describes that the use of image guidance techniques improves the accuracy (95.2%) of pedicle screw placement in spinal surgery compared to the subgroup without the use of navigation (90.3%)[10] .
A more recent review included a total of 30 studies by Mason[11]. These studies included 1973 patients in whom 9310 pedicle screws were inserted. Accurate placement was observed in 68% with conventional fluoroscopy, 84% with 2D fluoroscopic navigation, and 96% with 3D fluoroscopic navigation. The accuracy rates when using 3D navigation were also consistently higher throughout all individual spinal levels compared with 2D fluoroscopic navigation.
Significantly increased pedicle screw placement accuracy was also observed when navigation techniques in a meta-analysis by Tang in 2014 concerning accuracy of pedicle screw placement with or without image-guided navigation techniques (OR (Odds Ratio) =3.36 for perfect placed screws and OR=4.72 for screws placed in a “safe zone”, 732 patients with 4953 screws) [12].

In a review by Gelasis, the percentage of the screws fully contained in the pedicle ranged using free-hand technique ranged from 69 to 94%, with the aid of fluoroscopy from 28 to 85%, using CT navigation from 89 to 100% and using fluoroscopy-based navigation from 81 to 92%[13].

Table 2: Overview of publication related to accuracy of pedicle screw placements comparing conventional method and image-guided navigation.

First author	Study type	Measured item	Conventional method	Image-guided Navigation	Comment
Laine (2000)	Randomized study	Perforation rate Perforation>4 mm	13.4% (87% accuracy) 1.4% (4/277)	4.6% (95% accuracy) None	P =0.006 91 pts/ 496 screws (pre-op CT)
Rajasekaran (2007)	Randomized study	Pedicle breaches Penetrated the anterior or lateral cortex	23% (77% accuracy) 16%	2% (98% accuracy) 0.8%	P < 0.001 27 pts scoliosis/ 478 screws (Siemens Brainlab)
Kosmopoulos (2007)	Meta-analysis	Accuracy	90.3%	95.2%	130 studies 37337 screws
Mason (2014)	Review	Accuracy	68% conventional fluoro	84% 2D fluoro navigation 96% 3D fluoro navigation	2D/3D stat sign more accurate than conventional 3D stat. sign.

					More accurate than 2D 30 studies 1973 pts/ 9310 screws
Tang (2014)	Meta-analysis	Accuracy: Perfect screws Safe zones	Significant difference favoring procedure using navigation vs. non-navigated	OR=3.36 OR=4.72	P<0.00001 P<0.0001 12 studies 732 pts/ 4953 screws
Gelasis (2012)	Review	Accuracy	69 – 94% (free hand) 28 – 85% (fluoro)	89 – 100% (CT-navigated) 81 – 92% (fluoro navigated)	26 studies 1105 pts/ 6617 screws
Tian (2011)	Review and meta analysis	Pedicle screw violation	Significantly less pedicle screw violations in navigation group than conventional group	OR 95% CI* (0.32-0.60) CT based OR 95% CI (0.27-0.48) 2D fluoro OR 95% CI (0.09-0.38) 3D fluoro	P<0.01 P<0.01 P<0.01 Incl. 28 clinical studies
Summary		**Accuracy**	**28%-94%**	**81%-100%**	

*CI=Confidence Interval

Gebhard et al.[14] showed a clear reduction of radiation dose when using imaged guided surgery. They quantified the radiation doses during spine surgery in different types of image-guided surgery procedures (i.e., computerized tomography [CT] based and C-arm) compared to standard methods and the Iso-C3D C-arm (Siemens). The duration of radiation was reduced from 177 seconds in the standard spine procedure to 75 seconds in CT-based image-guided surgery. The radiation doses at the C-arm tube (source) are reduced from a median of 1091 mGy in the standard procedure versus 432 mGy in CT-based and 664 mGy in C-arm based guided surgery. In this study, the median dose of an Iso-C3D C-arm was 152 mGy.

Minimal invasive spine surgery

Besides using imaging guidance there is also a trend towards minimal invasive surgery. The advantages of minimal invasive spine surgery include; less post-operative pain, quicker recovery, reduced blood loss, less soft tissue damage, smaller surgical incisions, less scarring, improved function according to the Society for Minimally Invasive Spine Surgery[15]. For sacroiliac minimally invasive spine surgery operating room time, estimated blood loss, hospital length of stay is decreased significantly compared to open surgery. Furthermore, when matched for age, gender and a history of prior lumbar spinal fusion, postoperative pain scores were on average 3.0 points (95% CI 2.1 – 4.0) lower in minimal invasive surgery vs. open surgery (rANOVA $p < 0.001$)[16] . A literature review by Wong et al. of clinical outcomes and complications associated with the minimally invasive surgical decompression of lumbar stenosis reported a decreased blood loss, shorter operative time, shorter hospital duration, decreased postoperative narcotic requirement, decreased rate of infection and cerebrospinal fluid leak, and a decrease in time required for return to work[17]. Wong et al. mention in their literature review that despite many of the benefits from a minimally invasive spine surgery approach to lumbar stenosis, there remains a high rate of initial complications related to the steep learning curve of a new surgical technique.

Another subpopulation of patients that may benefit from minimally invasive spine surgery approaches would be obese patients. Obese patients tend to have longer operative times, increased blood loss, larger incisions and soft-tissue dissection for exposure, and increased complications (36–67% higher e.g. wound infections and pulmonary disease)[17] .

2.1. Evaluation of preclinical testing

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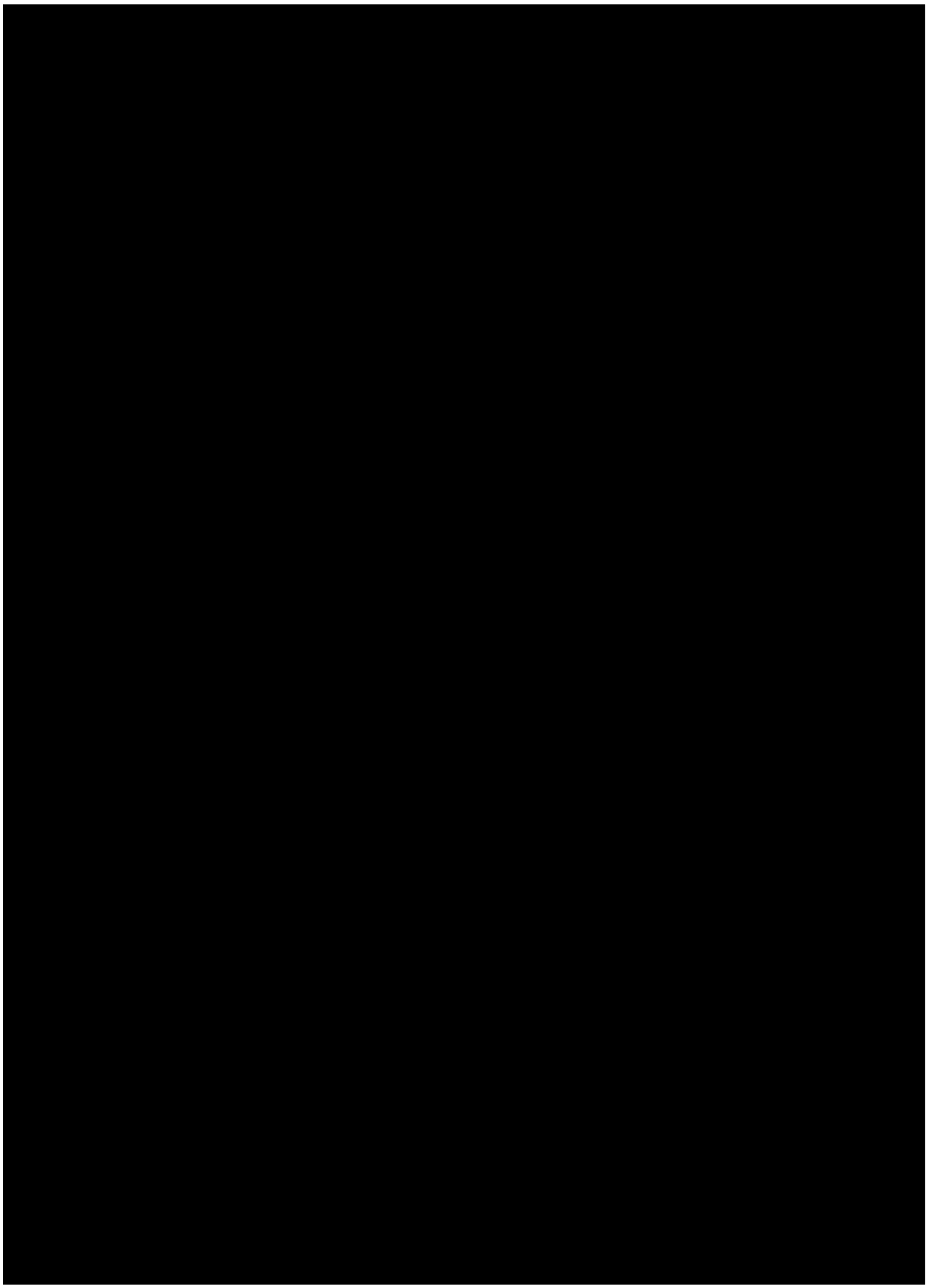

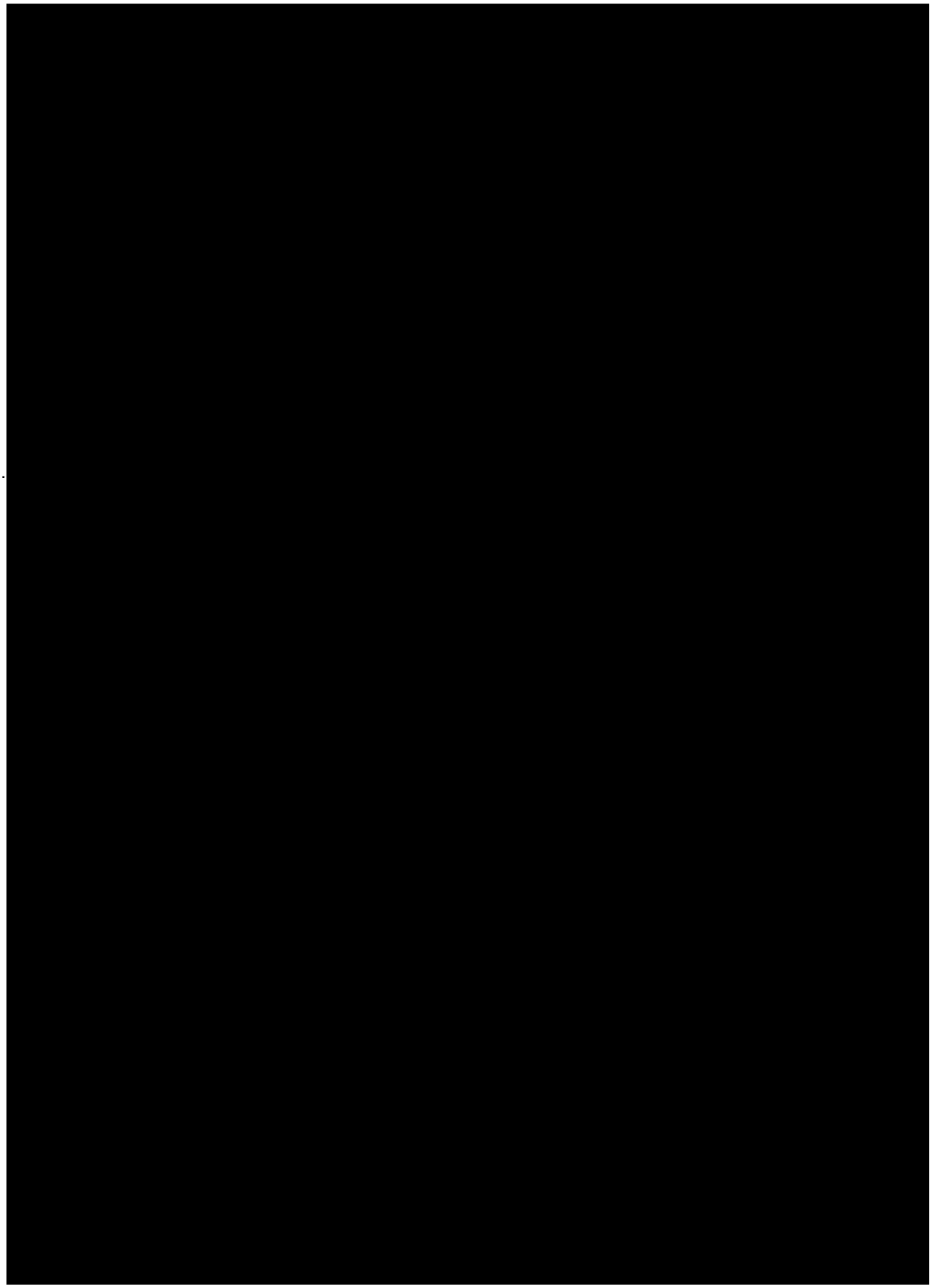

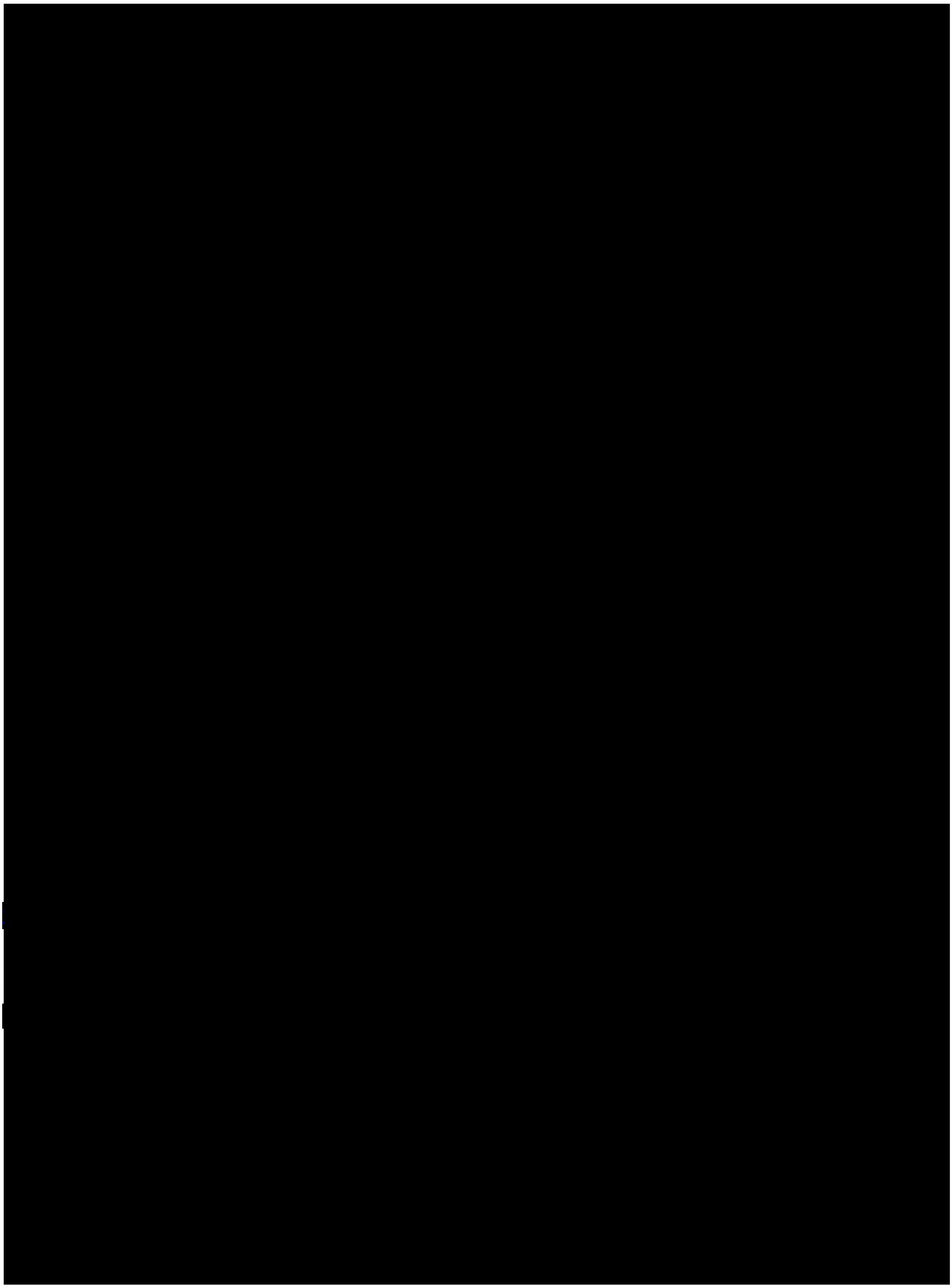

2.3. Conclusion of the justification for the design of the study

There is a clear need for accurate pedicle screw placement when stabilizing the spine to prevent damage to important structures. Image-guided navigation has shown to result in significantly accurate pedicle screw placement. With Surgical Navigation we have a similar image-guided technique as described in literature, but using real-time video overlay to align an instrument with a planned path.
The positive results of pre-clinical testing and a clinical study with Surgical Navigation has provided confidence to perform a clinical study related to pedicle screw placement in humans to further evaluate Surgical Navigation. An observational pilot study using Surgical Navigation in a small group of patients undergoing a spine surgery involving pedicle screw placement is the next step in evaluating Surgical Navigation in clinical use. An observational, non-comparative study design has been chosen based on the primary objective of the study (i.e., to estimate the overall proportion of screws accurately placed with the research procedure). The outcome of the study will provide for estimation of the mean accuracy and confidence intervals for Surgical Navigation system. These result will be compared with earlier found results in the pre-clinical testing and may be used to design future studies.

Alternative studies design were evaluated but not chosen for the following reasons:

- Based on previous literature studies with procedure where pedicle screws are placed, there is a large variability between the accuracy of placing pedicle screws (mostly 68%-94%, one study even reported 28% accuracy for the standard of care method (See table 1 in the Investigator Brochure). This is due to differences in pedicle width in the different areas in the spine (cervical/higher thoracic versus lumbar) and deformation of spine (especially with scoliotic patients). So there is an expected difference for the outcome for pedicle screw placement accuracy between different subjects and between different screws within a subject.
- Randomizing treatment groups, during procedure, within a patient (i.e., left versus right side) for a paired study design that control for the between subject variability is cumbersome and may affect the

normal workflow for the procedure. Also, such step will increase the procedure time where patients are under sedation and lying with a large incision (increasing possible infections).

- Randomizing treatment groups to different subjects (i.e., standard of care and surgical navigation) may require extremely large study as the study will need to account for the variability within and between subjects. Also, the outcome of such comparison may not truly represent the therapy rather the patient condition.

2.4. Purpose of the study

The purpose of the study is to estimate the accuracy of the use of Surgical Navigation during spine procedures. Surgical Navigation is expected to provide assistance to the performing physician in aligning an instrument with a virtual path, planned on 3D image of the anatomy and overlaid on a live video image of the area of interest. Alignment of the instrument with the virtual planned path will potentially lead to placing the instrument.at the desired location. Therefore the primary objective of the study is to estimate the accuracy of placement of pedicle screw with the assistance of Surgical Navigation. Secondary objectives will further asses other aspects of the use of Surgical Navigation in spine procedures, such as procedure time, usability (see APPENDIX III: USABILITY TESTING BACKGROUND) and workflow, patient dose and safety.

3. RISKS AND BENEFITS OF THE INVESTIGATIONAL DEVICE AND CLINICAL INVESTIGATION

The risk assessment process that Philips follows is in accordance with ISO 14971.This will ensure that the level of risk is assessed and risk mitigation measures (i.e. acceptable risk) are in place prior to start of the study.

Participation in the clinical study will provide no additional risk other than using the Surgical Navigation.

There are no possible interactions with concomitant medical treatments.

A final risk assessment has been performed. The overall residual safety risk for the investigational device Surgical Navigation for the purpose of the clinical study is assessed to be acceptable. The investigational device Surgical Navigation is safe for clinical use based on the assessment of the individual risk profiles, the overall residual risks and supported by the earlier clinical study performed.

To facilitate safe and effective operation of the system by a trained healthcare professional, instructions for use are provided as part of the device labelling, as well as training at system handover.

The performed final safety assessment concluded that the potential benefits, as outlined above, clearly outweigh any potential risks associated with the use of this device in the clinical study.

Other documents which are related to the risk management activities (e.g. informed consent, Investigator Brochure, IFU) are in agreement with both the Risk Management File and the final conclusions given in the Risk Management Report

4. OBJECTIVES

4.1. Primary objective

The primary objective of this clinical investigation is to estimate the accuracy of pedicle screw placement using Surgical Navigation on post-procedural CBCT:

Screw placement will be evaluated using a slightly adapted Gertzbein[4] classification for pedicle screw breach as follows:
grade 0 = breach 0 mm
grade 1 = lumbar and thoracic < 2 mm, cervical <1 mm breach distance
grade 2 = lumbar and thoracic 2-4 mm, cervical 1-2 mm breach distance
grade 3 = lumbar and thoracic > 4 mm, cervical >2 mm breach distance.

Accuracy will be reported by the proportion of pedicles having either grade 0 or 1.

4.2. Secondary objective(s)

The secondary objectives are:

1) To estimate the procedure time.
2) To estimate the average time to insert a pedicle screw.
3) To estimate the length of hospitalization (LOH)
4) Collect System Usability Scale (SUS) and assess the clinical workflow related to easiness to work, image quality, real-time image update, preparation of patient tracking, confidence in image guidance, access planning, 3D segmentation, motion compensation, identify unknown potential use errors and evaluate risk controls.
5) To estimate radiation dose (Dose Area Product (DAP) and Air Kerma (AK)) delivered to patient for:
    a. Total procedure
    b. During preparation and acquisition of CBCT for path planning
    c. During screw/instrument placement (using fluoro).

d. During preparation and acquisition of CBCT for confirmation
e. Average procedure dose per planned path

6) To estimate the total radiation dose (effective dose) received by operator, if DoseAware Xtend is available.
7) To describe procedure related complications
8) Report all adverse events
9) Report all adverse device effects
10) Report all device deficiencies that could have led to a serious adverse event

The objectives are descriptive in nature and are intended to provide additional information. There will be no pass or fail criteria.

5. STUDY DESIGN

5.1. General

This is a prospectively planned, single arm, single center study designed to estimate the accuracy of the pedicle screw placement using the Surgical Navigation procedure in patients undergoing pedicle screw fixation surgery. Accuracy will be reported by the proportion of pedicles having either grade 0 or 1 according to a slightly adapted Gertzbein[4] classification. The slightly adapted Gertzbein[4] classification for pedicle screw breach is defined as follows:

- grade 0 = breach 0 mm
- grade 1 = lumbar and thoracic < 2 mm, cervical <1 mm breach distance
- grade 2 = lumbar and thoracic 2-4 mm, cervical 1-2 mm breach distance
- grade 3 = lumbar and thoracic > 4 mm, cervical >2 mm breach distance.

The proportion of screws placed according to grade 0-3 will be estimated overall, and by region (e.g., cervical, lumbar, and thoracic). In addition, the number of lateral or medial perforations, the distance of the longitudinal axis of the screw and the planned path at the smallest diameter of the pedicle (mm), and the largest distance between screw tip and planned target of screw (mm) will be reported.

5.2. Investigational device exposure

Surgical Navigation is used for image-guided navigation during pedicle screw placements procedures for subjects participating in the study.

There are no additional devices or medications required for the study.

5.3. Subjects

5.3.1. In- and exclusion criteria

Subjects participating in the study will be carefully selected based on the next inclusion and exclusion criteria.

5.3.1.1. *Inclusion criteria*

- Subject will be undergoing a spine surgery with pedicle screw placement
- Subject is 16 years of age or older
- Subject is able to give informed consent

5.3.1.2. Exclusion criteria

- Subject participates in a potentially confounding device or drug trial during the course of the study.
- Subject meets an exclusion criteria according to national law (e.g. pregnant woman, breast feeding woman)

5.3.2. Enrollment and duration

Subjects are considered to be enrolled in the clinical investigation after they have signed the informed consent form. No study procedures will be performed before this moment.

The subjects will be followed-up for this study until hospital discharge. After this the patient will be followed up according to standard of care outside the study.

The total duration of the study is expected to take approximately 1 year

5.3.3. Number of subjects

In total 240 screws placement are needed. It is expected that approximately 15 to 25 subjects with pedicle screw surgery are necessary to collect sufficient data for the evaluation of the primary and secondary objectives of this clinical investigation. After the first two subjects have been treated with pedicle screws there will be a delay of at least 1 week until the third and fourth subjects will be undergoing the procedure with Surgical Navigation. After subject one to four have been treated and the DMC/DSMB have been given recommendations of continuation of the study then there is no limit on how many subjects can be treated during one day. Enrollment of subjects will be stopped after approximately 240 screws are placed. This is a common number of screws used in studies showing accuracy of pedicle screw placement in the cervical[28]. The enrollment period is expected to last for 7 months.

See section 6 Statistical considerations for more detail on the number of subjects.

5.3.4. Subject withdrawal or discontinuation

Subjects can withdraw informed consent at any time during the clinical investigation. There are no specific criteria for subject withdrawal or discontinuation.

5.4. Procedures

Pedicle screw placement

Pedicle screws will be placed using Surgical Navigation image guidance during spine surgery. The specific clinical investigation related steps for this spine surgery are (see also Figure 8):

- Sterile drapes compatible with the Allura and Surgical Navigation with transparent windows are placed over the detector.
- Several optical markers stickers (4-6 depending on the size of the region of interest) are placed at the back of the patient around the area of interest.
- A 3D CT like image is made (CBCT) of the relevant vertebrae.
- The spine image can be segmented using Surgical Navigation, if desired.
- The optimal path for the screw/instrument is planned in the CBCT volume.
- The optical view of Surgical Navigation is used to align the instrument (e.g. K-wires, screws instrumentation) with the planned path at the entry point. Progression view (view perpendicular to the planned path) using fluoro can be used during insertion of the screw, if desired. With this progression view function, the user can check on an x-ray image the actual placement of the screw at each moment in the procedure.
- The pedicle screws/instrumentation are further inserted in the vertebra using tools according to standard of care.
- Acquisition of a CBCT showing all placed pedicle screws/instrumentation to check the success of the procedure. This CBCT replaces the standard post-operative CT to check the procedure.
  For pedicle screw placement: Like in normal clinical practice, the necessity for revision of a pedicle screws is determined based on 3D information. This CBCT with the pedicle screws will be used to determine the accuracy of pedicle screw placement for the objectives of this study. The physician will indicate the classification according to the classification system (grade 0-3, see section 4.1). This classification can be done post-procedure.
- Time of the total procedure will be measured.
- Patient and occupational dose data will be collected using Surgical Navigation and DoseAware Xtend (if available at the hospital), respectively.

Patients participating in this study are subject to follow-up until hospital discharge to collect the length of hospital stay.

All other things are the same as the current standard of care.

All post-procedural CBCT acquisitions will be evaluated by an independent reviewer (neurosurgeon, orthopedic surgeon or spine surgeon experienced in pedicle screw placements) to determine the accuracy of pedicle screw placement according to the modified Gertzbein grading system (grade 0-3, see section 4.1) and direction (lateral/medial breach).
Furthermore, the distance (mm) between the following two points will be measured:

- The planned path and screw axis at smallest pedicle diameter
- The planned path and at the tip of the screw

The classification by the independent reviewer will be used for the objectives.

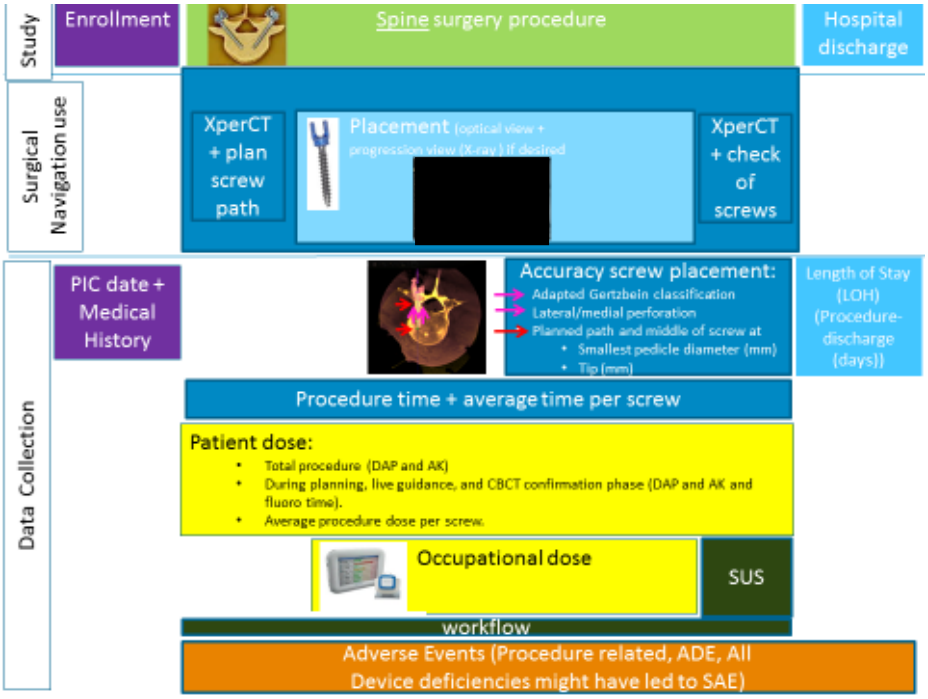

Figure 8: Flowchart for patient undergoing pedicle screw placement

Workflow feedback and usability information
Observations related to the workflow for the spine procedure will be performed by a Philips representative during some of the procedures. Workflow feedback will also be obtained through a short interview with the physician performing the procedure.
At the end of the study the physician(s) performing the procedure will be requested to complete a System Usability Scale (SUS) questionnaire to obtain general information related to the usability of Surgical Navigation related to these spine procedures.

5.5. Monitoring Plan

A detailed plan for monitoring arrangement will be described separately from the Clinical Investigation Plan.

Monitoring will be performed by a trained person appointed by Philips to ensure compliance with the Clinical investigation plan, applicable national regulations and international standards, patient safety and data validity. The Sponsor, Philips, may designate one or more individuals to monitor the progress of a clinical study. The Sponsor may also delegate the monitoring responsibilities to a third party. However, the Sponsor remains ultimately responsible for the conduct of the study. The Institution is responsible for the appropriate de-identification of subject data. The investigational site should provide access to the source data of the subjects.

The first visit will occur as soon as possible after the first subject is enrolled at each study site. The monitoring schedule is based on the following considerations: enrollment rate, study compliance at the center, magnitude of data corrections required, complexity of the investigation, IRB/MEC request, audit/inspection.

Critical data and processes will be monitored for this study prior to clinical report completion based on a risk based monitoring approach. Dependent on the risk a high or lower sample will be monitored.
The monitor will review critical clinical data that affect study endpoints.

A close-out visit at a site that has enrolled subjects will be conducted once the site has completed collecting data for the study.

The monitor activities include:

- Check that the study is conducted, recorded and reported in compliance with this clinical investigation plan, and applicable regulations. Acts to oversee the progress of the study.
- Check signed and dated informed consent of the subjects and check that this is signed before any study-related procedures are undertaken.
- Ensure that essential documents (e.g. contract, MEC approval) are maintained in the Investigator Site File.
- Ensure recording of deviations from protocol and store in Investigator Site File or CRF.
- Ensure that all adverse events and device deficiencies are reported to the sponsor, and all serious adverse events and device deficiencies that could have led to a serious adverse device effect are reported to the sponsor without unjustified delay.
- Ensure that adverse event and device deficiency are reported to the MEC/IRB, if required.
- Ensure that the principal investigator is informed and knowledgeable of all relevant document updates concerning the clinical investigation (e.g. clinical investigation plan and Investigator Brochure). Ensure that amendments to the protocol and/or Investigators Brochure are provided to the MEC/IRB by the principal investigator.
- Ensure device accountability and check unapproved use outside the study.
- Source data verification is anticipated.

Names of the monitor(s) can be found in Appendix II: List of monitor(s) of this protocol. An update of this list can be provided to the site under separate cover.

5.5.1. Maintenance and calibration

The equipment relevant for the dose measurements during the clinical investigation are the Allura and DoseAwareExtend. Allura is calibrated at the time of installation and mostly after one year. DoseAwareExtend is calibrated once before providing it to the hospital. Since the duration of the study is expected to be less than one year after installation, both will not be monitored for calibration during the course of the study.

The optical cameras and the X-ray system in the Allura system will be calibrated during the installation in the hospital. Regular check will be performed by trained Philips personnel during the clinical study if recalibration of the camera and X-ray system alignment is needed.

6. STATISTICAL CONSIDERATIONS

6.1. Sample Size Justification

Mason et al (2014) reported on a meta-analysis of 30 studies evaluating screw placement using 2D, 3D, and conventional fluoroscopic image guidance systems. Using the conventional fluoroscopy, 2532 of 3719 screws were inserted accurately (68.1% accuracy); with 2D fluoroscopic navigation, 1031 of 1223 screws were inserted accurately (84.3% accuracy); and with 3D fluoroscopic navigation, 4170 of 4368 screws were inserted accurately (95.5% accuracy).

In a human cadaver study using Surgical Navigation system the accuracy was 85 % (95% CI of 72%, 95% and 74%, 96% using vertebras within a cadaver as a cluster), compared to 64% (95% CI of 44%, 77%) for the conventional free-hand method. In another human cadaver feasibility study, 21 screws were placed using the fluoroscopy guidance system and another 21 screws using Surgical Navigation system. In 95% of insertions (20) the pedicle screws were placed in accordance with the predefined paths using the Surgical Navigation compared to 71% of the insertions with fluoro-guidance system.

Assuming that the screw placement accuracy for this study will be similar to that observed in the cadaver study (i.e., 85%), a sample size of 240 screws will be required to estimate a 95% two-sided confidence interval so that the lower bound of the 95% CI is greater than the upper bound of the 95% CI observed for the cadaver study (i.e., 64% with upper bound of 95% CI of 77 with approximately 80% power (%) (i.e., approximately 5% Half Width). Assuming that the subjects will have 2 to 10 vertebrae's treated and the assumption that the majority of the patients will be scoliotic patients, approximately 15 to 25 patients will be needed to reach 240 screw placements.
Any deviation from the planned analysis described below will be documented with justification in the final clinical end report.

6.2. General Consideration

The primary analysis of safety and efficacy will be performed including all subjects who underwent treatment (ITT population). All variables will be summarized by descriptive statistics The statistics for continuous variables includes mean, median, standard deviation, 95% confidence interval for the means, and the number of observations. For categorical variables, number events, event rate, and 95% confidence interval for the event rate will be presented.

6.3. Subject disposition

Subject disposition, including the total number of subjects evaluated will be presented. In addition, a listing will be provided with the reasons for why the subject was not evaluated.

6.4. Demographics and Baseline Characteristics

Basic subject characteristics such as age, gender, height and weight will be summarized. In addition, the main reason for surgery will be presented.

6.5. Primary objective

Objective
The primary objective of this clinical investigation is to estimate the accuracy of pedicle screw placement using Surgical Navigation based on post-procedural CBCT:

Endpoint
The primary endpoint is the accuracy of screw placement. Screw placement will be evaluated using the slightly adapted Gertzbein[4] classification for pedicle screw breach as follows:

- grade 0 = breach 0 mm
- grade 1 = lumbar and thoracic < 2 mm, cervical <1 mm breach distance
- grade 2 = lumbar and thoracic 2-4 mm, cervical 1-2 mm breach distance
- grade 3 = lumbar and thoracic > 4 mm, cervical >2 mm breach distance

Accuracy is defined as the proportion of screws with Gertzbein grade 0 or 1. The proportion of screws accurately placed will be estimated overall, and by region (e.g., cervical, lumbar, and thoracic).

In addition, the number of lateral or medial perforations, the distance of the longitudinal axis of the screw and the planned path at the smallest diameter of the pedicle (mm), and the largest distance between screw tip and planned target of screw (mm) will be reported.
See Appendix V: Background information primary objective for more information on the primary objective.

Analysis
The primary objective for this study is to estimate the overall proportion of screws accurately placed. All subjects who underwent treatment (ITT population) will be included in the primary efficacy analysis. Analysis will be performed assuming independence among different screws within a subject using Exact Clopper-Pearson 95% confidence interval. In addition, analysis will be performed using each subject as the unit for analysis. For this analysis, a two-sided 95% CI calculated for the accuracy of screw placement will be calculated using clustered binary data methodology as described by Zhou (2011)[29].

In addition, the proportion of screws accurately placed will be summarized by region (e.g., cervical, lumbar, and thoracic) and by grade 0-3. The 95%confidence interval will be presented.

6.6. Secondary objectives

6.6.1. Secondary objective: Procedure Time

Objective
To estimate the procedure time.

Endpoint
Besides the procedure time, also the time for preparation steps will be measured (see Table 4 for more specification).

Table 4: Time measurement

Endpoint	Measured by the time between
Total preparation time	Nurse in room to prepare room – Time-out
Preparation time before patient on table	Nurse in room to prepare room – Patient on table
Patient preparation time	Patient on table-Start anesthesia
Anesthesia time	Start anesthesia-End anesthesia
Patient preparation after anesthesia + use system for patient preparation	End anesthesia-Time-out
Procedure time	Incision time - Wound closure

Analysis:
Summary statistics will be calculated using Kaplan-Meier procedure.

6.6.2. Secondary objective: Time to insert a pedicle screw

Objective
To estimate the average time to insert a pedicle screw.

Endpoint
The time to insert a screw is calculated from:

- Start time of the CBCT to plan the path until last screw placed, divided by the number of screws.
- Start time from choosing the path to place the first screw until last screw placed, divided by the number of screws

The first represent the time it takes to place a screw taking into account the path planning and the second represent just the time it takes to place a screw during the live guidance work step. Time points are logged via the Surgical Navigation.

Analysis
Summary statistics will be calculated using Kaplan-Meier procedure.

6.6.3. Secondary objective: Length of hospital stay

Objective
To estimate the length of hospitalization (LOH)

Endpoint
The endpoint is length of hospitalization. This is calculated by the day of procedure until hospital discharge in days.

Analysis.
Summary statistics will be calculated using Kaplan-Meier procedure.

6.6.4. Secondary objective: System usability

Objective
Collect System Usability Scale (SUS) and assess the clinical workflow related to easiness to work, image quality, real-time image update, preparation of patient tracking, confidence in image guidance, access

planning, 3D segmentation, motion compensation, identify unknown potential use errors and evaluate risk controls.

Endpoint
The endpoint is System Usability Scale measured at the end of the study. Furthermore the clinical workflow will be described.

All users that entirely completed the SUS questionnaire will be included in the analysis.

Analysis
The SUS scores of each respondent will be categorized according to the SUS score.
Calculation of the scoring SUS will be done according to the following principle:

- For odd items: subtract one from the user response.
- For even-numbered items: subtract the user responses from 5
- This scales all values from 0 to 4 (with four being the most positive response).
- Add up the converted responses for each user and multiply that total by 2.5. This converts the range of possible values from 0 to 100 instead of from 0 to 40.

A SUS score above a 68 would be considered above average and anything below 68 is below average.

6.6.5. Secondary objective: Patient Dose

Objective
To estimate radiation dose (Dose Area Product (DAP) and Air Kerma (AK)) delivered to patient for:
Total procedure

a) During preparation and acquisition of CBCT for path planning
b) During screw/instrument placement (using fluoro).
c) During preparation and acquisition of CBCT for confirmation
d) Average procedure dose per planned path

Endpoint
The endpoint is Radiation Dose (DAP and AK) delivered to the patient:

a) For Total procedure (including CBCT and fluoro)
b) During preparation and acquisition of CBCT for path planning
c) During screw/instrument placement (using fluoro) (DAP and AK and fluoro time).
d) During preparation and acquisition of CBCT for confirmation
e) Average procedure dose per planned path. Calculated based on dose described at b) and c) divided by the number of screws. Average procedure dose per planned path will also be reported per region (e.g. cervical, thoracic and lumbar)

Analysis
All subjects who underwent the procedure will be included in this analysis.
Radiation dose will be summarized using descriptive statistics. Mean, median, standard deviation and 95% confidence interval for the mean will be presented.

6.6.6. Secondary objective: Occupational dose

Objective

11) To estimate the total radiation dose (effective dose) received by operator, if DoseAware Xtend is available.

Endpoint
The endpoint is occupational dose measured via DoseAware Xtend. DoseAware Xtend is a CE labeled device. DoseAware Xtend measures real-time dose for the operator in the interventional suite via the use of Personal Dose Meter (PDM). The PDM is worn by the operator. This badge measures scatter radiation and transmits this information.

Analysis
This objective will only be done when DoseAware Xtend is present at a site.

Occupational dose will be summarized using descriptive statistics. Mean, median, standard deviation and 95% confidence interval for the mean will be presented.

6.6.7. Secondary objective: Procedure related complications

Objective

12) To describe procedure related complications

Endpoint

Procedure related complications
Definition of complication: An adverse event that results in invasive intervention. Intravenous (IV) and intramuscular (IM) drug therapies are considered as invasive treatment.

Analysis

All procedure related complications will be presented in a tabular format.

6.6.8. Secondary objective: Adverse events

Objective

Report all adverse events

Endpoint

Adverse events, including information of the seriousness, treatment needed, resolution and relevant judgment concerning the causal relationship with the investigational devices or procedure will be summarized for safety information.

Analysis

All adverse events will be presented in a tabular format.

6.6.9. Secondary objective: Adverse Device Effects

Objective

Report all adverse device effects

Endpoint

Adverse device effects, including information of the seriousness, treatment needed, resolution and relevant judgment concerning the causal relationship with the investigational devices or procedure will be summarized for safety information.

Analysis

All adverse device effects will be presented in a tabular format.

6.6.10. Secondary objective: Device Deficiencies that could have led to Serious Adverse Event

Objective

Report all device deficiencies that could have led to a serious adverse event

Endpoint

Device deficiencies that could have led to Serious Adverse Events, including any corrective actions taken during the study, if any, will be summarized for safety information.

Analysis

All device deficiency that could have led to a serious adverse device effect will be presented in tabular format.

7. DATA MANAGEMENT

Electronic Case Report Form (e-CRF) will be used to collect medical history, subjects demographics, procedure related information, protocol deviations, adverse events and device deficiencies. The e-CRF will be used for data review, data cleaning and issuing and resolving queries. This e-CRF is a web-based e-CRF

which is password protected and is 21 CFR part 11 compliant. At the end of the study the data will be stored as a frozen dataset and will be retained. Workflow analysis and SUS questionnaire will be performed separately from the e-CRF.

The e-CRF data from the subjects will be key-coded (pseudonymized). The information related to the subjects (like name) is kept separately in the enrollment log at the hospital. Date and time of the procedure and date of discharge will be collected. Patient dose data will not contain any patient names or numbers. Procedure date and time will be used to link the dose data to the corresponding CRF data.
Exported (image) data will be de-identified. The remaining data will be de-identified.
The data will be collected and stored in a secure location.

7.1. Retention period

The investigator shall maintain the records related to this study during the investigation and for a period after the study according to national regulations (5 years)
Philips will maintain the records for a period of device End of Life (EoL) plus 15 years.

The sponsor and principal investigator shall take measures to prevent accidental or premature destruction of these documents.

8. AMENDMENTS TO THE CLINICAL INVESTIGATION PLAN AND INFORMED CONSENT

Amendment to the Clinical investigational plan and the informed consent shall be notified to, or approved by the Medical Ethics Committee (MEC) and regulatory authority. The version number and date of amendments shall be documented.
Significant changes (such as device modifications, study procedures) shall be discussed with the principal investigator prior approval. All changes will be documented with a justification and described in the latest version of the Clinical Investigation Plan.

9. DEVIATIONS FROM THE CLINICAL INVESTIGATION PLAN

The Investigator is not allowed to deviate from the Clinical Investigation Plan or to enroll subjects that do not comply with all inclusion and exclusion criteria. Under emergency circumstances, deviations from the Clinical Investigation Plan to protect the rights, safety and well-being of human subjects may proceed without prior approval of the sponsor and the MEC. Such deviations shall be documented and reported to the sponsor and the MEC as soon as possible
All deviations from the Clinical Investigation Plan will be documented with date, subject, reason, actions taken and if the deviation affects subject's rights, safety and well-being or the scientific integrity of the clinical Investigation. The deviation shall be notified to the Sponsor as soon as possible via the e-CRF. Deviations will be reviewed by the sponsor and in case of serious or repetitive deviations a corrective action plan may represent a need to initiate a corrective action plan with the principal investigator. In some cases, necessitate suspension of enrollment at the site or ultimately the principal investigator will be disqualified.

10. DEVICE ACCOUNTABILITY

Access to the investigational device shall be controlled and the investigational devices shall be used only in the clinical investigation and according to the Clinical Investigation Plan.

The sponsor shall keep records to document the physical location of all investigational devices from shipment of investigational device to the Investigation site until return or disposal.

The principal investigator shall keep records documenting the receipt, installation, use, return and disposal of the investigational device, including date of receipt, identification of each investigational device, the date of use, and date on which the investigational device was returned/disposed.

11. STATEMENTS OF COMPLIANCE

This clinical Investigation shall be conducted in accordance with the clinical Investigation plan, and with the ethical principles that have their origin in the Declaration of Helsinki and all applicable regional and/or

national regulations. Furthermore, in Europe this clinical Investigation shall be conducted in accordance with the International Standards ISO 14155 Clinical investigation of medical devices for human subjects – Good clinical practice and the Medical Device Directive (MDD). Furthermore all investigators will complete financial disclosures, as outlined in the 21 CFR part 54.

This clinical Investigation shall not be started prior to obtaining a favorable opinion from a Medical Ethics Committee (MEC) and Regulatory authority, if required. Any additional requirements imposed by the MEC/IRB and/or regulatory authority shall be followed.

Insurance shall be provided for the subjects participating in this clinical trial according to local law.

12. INFORMED CONSENT PROCESS

Informed consent will be obtained from every subject in writing by the Investigator or his authorized designee before the clinical Investigation is started. The subject will be informed both orally and in writing about all aspects that are relevant to the subject's decision to participate in the trial, including the trial procedures and risks and benefits of participation in the clinical investigation. Ample time should be provided for the subject to read and understand the informed consent form and to consider participation. The informed consent will include personally dated signatures of the subject and the principal investigator or an authorized designee responsible for conducting the informed consent process. A copy of the signed and dated informed consent form and any other written information will be provided to the subject.

If new information becomes available that might significantly affect the subject's future health and medical care, it shall be provided to the subjects in written form. If relevant, subject shall be asked to reconfirm their continuing informed consent in writing.

13. ADVERSE EVENT REPORTING

13.1. Definitions

Adverse Event

An Adverse Event (AE) is defined as any untoward medical occurrence, unintended disease or injury or any untoward clinical signs (including an abnormal laboratory finding) in subjects, users or other persons whether or not related to the investigational device.

NOTE 1 This definition includes events related to the investigational medical device or the comparator.
NOTE 2 This definition includes events related to the procedures involved.
NOTE 3 For users or other persons, this definition is restricted to events related to investigational medical devices.

Adverse Device Effect

An Adverse Device Effect (ADE) is defined as an adverse event related to the use of an investigational medical device. Note 1. This includes any adverse event resulting from insufficiencies or inadequacies in the instructions for use, the deployment, the implantation, the installation, the operation, or any malfunction of the investigational medical device. Note 2. This includes and any event that is a result of a use error or intentional abnormal of the investigational device.

Serious Adverse Event

A Serious Adverse Event (SAE) is an adverse event that
a) led to death, injury or permanent impairment to a body structure or body function
b) led to serious deterioration in the health of the subject, that either resulted in
    1) a life-threatening illness or injury, or
    2) a permanent impairment of a body structure or a body function, or
    3) in-patient hospitalization or prolongation of existing hospitalization, or
medical or surgical intervention to prevent life-threatening illness c) led to foetal distress, foetal death or a congenital abnormality or birth defect

NOTE Planned hospitalization for a pre-existing condition, or a procedure required by the Clinical Investigation Plan, without a serious deterioration in health, is not considered a serious adverse event.

Serious Adverse Device Effect (SADE)
Adverse device effect that resulted in any of the consequences characteristic of a serious adverse event

Unanticipated Serious Adverse Device Effect
Unanticipated Serious Adverse Device Effect (USADE) is a serious adverse device effect which by its nature, incidence, severity or outcome has not been identified in the current version of the risk analysis report
NOTE Anticipated serious adverse device effect (ASADE) is an effect which by its nature, incidence, severity or outcome has been previously identified in the risk analysis report.

Device Deficiency
Inadequacy of an investigational medical device with respect to its identity, quality, durability, reliability, safety or performance. This may include malfunctions, use error, or inadequacy in the information supplied by the manufacturer.

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13.2. Reporting

The following are considered reportable events:

- Any SAE;
- Any Device deficiency that could have led to a SAE if
  - a) suitable action had not been taken or;
  - b) intervention had not been made or;
  - c) if circumstances had been less fortunate;
  - New findings/updates in relation to already reported events.

The sponsor will report to the Competent Authority (MPA):

- All reportable events as described above, which indicate imminent risk of death, serious injury, or serious illness and requires prompt remedial actions for other patients/subjects, users or other persons, or a new finding to it: immediately, but not later than 2 calendar days following the date of awareness of the sponsor of a new reportable event or new information in relation to an already reported event.

- Any other reportable event or a new finding/update to it: immediately, but not later than 7 calendar days following the date of awareness of the sponsor of a new reportable event or new information in relation to an already reported event.

.

The investigator shall document these reportable events in the e-CRF which must be provided to the sponsor immediately, but not later than 3 calendar days after the investigational study site personnel's awareness of the event.

In Appendix II: List of monitor(s) provided by the sponsor which should be contacted by the investigator in the event of a reportable event is given.

- Other adverse events shall be recorded on the adverse event forms in the e-CRF. The Sponsor and Monitor can request access to this information at any time.

The CRF will include the following information for adverse event reporting: date of the adverse event, description, actions taken, resolution, assessment of both the seriousness and the relationship to Surgical Navigation application and procedure. It will be determined if the SAE is related to the device or procedure and classified according to five different levels of casualty:

- Not related (relationship to the device or procedures);
- Unlikely (relationship with use of the device seems not relevant and/or the event can be reasonably explained by another cause);
- Possible (the relationship with the use of the device is weak but cannot be ruled out completely);
- Probable (relationship with use of the device seems relevant and/or the event cannot be reasonably explained by another cause);

- Cause relationship (the serious event is associated with the device or the procedures beyond reasonable doubt).

Information collected for device deficiencies are: date of device deficiency, whether this could have led to a Serious Adverse Device Effect (SADE) if a) suitable action had not been taken or b) intervention had not been made or c) if circumstances had been less fortunate.
The investigator should report to the MEC and/or competent authority these serious adverse events and device deficiencies that might have led to a serious adverse device effect, if required by MEC or competent authority.

13.3. Xxxxxxxxxxxxxxxxxxxxxxxxxxxx

[redacted]

13.4. Unavoidable adverse events

The following unavoidable adverse events are very common during the procedures performed in this clinical trial. Unavoidable adverse events do not need to be reported if occurred in the timeframe indicated below.

Table 6: Unavoidable adverse events

Unavoidable adverse event	Time frame
Incision pain/bruising after the intervention at point of entrance for the	2 weeks

intervention	

13.5. Data Monitoring Committee

Since the study will include subjects with the age of 16 years and older an independent Data Monitoring Committee (DMC/DSMB) will review all adverse events and all serious adverse events during the whole study period. The DMC/DSMB will review all adverse events that may occur after the first two subject have been treated. The DMC will provide a recommendation of continuation of the study. The third and fourth subject could be included 1 week after the first two subject have been treated with pedicle screws. The DMC/DSMB will review again and will provide a recommendation of continuation of the study.
The DMC/DSMB will have regular meetings to evaluate any kind of events and provide recommendations regarding continuation of the study.

14. EARLY TERMINATION OR SUSPENSION OF THE CLINICAL INVESTIGATION

There are no provisions or interim analyses planned that can result in an early termination of the trial.
Any signs of unknown or increased risks for the subjects will be discussed by the sponsor and investigator to assess the impact on the subjects and clinical investigation. Serious or repetitive occurrence of deviations from study protocol or non-compliance with regulations may also be reason for early termination or suspension of a study site.

15. PUBLICATION POLICY

It is the intention of the investigator and sponsor to submit the clinical investigation data for publication. Prior to submission, claims on intellectual property will be assessed.

This study will also be registered on clinicaltrial.gov before first enrollment.

16. DEFINITIONS AND ABBREVIATIONS

Abbreviations	Explanation of abbreviation
ADE	Adverse Device Effect
AE	Adverse Event
AK	Air Kerma
CBCT	Cone Beam Computed Tomography
CFR	Code Federal Regulations
CI	Confidence Interval
CRF	Case Report Form
DAP	Dose Area Product
DMC/DSMB	Data Monitoring Committee
e-CRF	Electronic Case Report Form
Entry point	The entry point is the point where the instrument (e.g. pedicle screws, screwdrivers, needle) will enter the body. The entry point can be the skin or the vertebrae, dependent on the type of procedure (Minimally invasive surgery or open surgery, respectively).
IFU	Instructions for Use
IM	Intramuscular
ISO	International Organization for Standardization
IV	Intravenous
MEC	Medical Ethic Committee
MDD	Medical Device Directive
OR	Odds Ratio
Placement	The actual position of the screw in the human body
SAE	Serious Adverse Event
SUS	System Usability Scale

USADE	Unanticipated Serious Adverse Device Effect

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APPENDIX I: LIST OF INVESTIGATORS AND SITES

Update of this list can be provided to the investigation site under separate cover.

Table 7: List of principle Investigators

Name Clinical Coordinating Investigator	Name and address investigation site
Adrian Elmi-Terander, MD Neurosurgeon	Karolinska University Hospital Department of Neurosurgery SE-171 76 Stockholm [redacted]

Table 8: Independent reviewers

Name and address other Institution(s)
Name of the independent reviewers is pending

APPENDIX II: LIST OF MONITOR(S)/CLINICAL SCIENTIST

Update of this list can be provided to the Investigational sites under separate cover.

Table 9: List of monitor/clinical scientist

Name Monitor(s)/Clinical Scientist	Contact Information of Monitors
[redacted] Clinical Science study manager Emergency contact	Philips Healthcare, Image-guided Therapy Systems Veenpluis 4-6 5684 PC Best The Netherlands [redacted]
[redacted] Drazenko Babic Clinical Fellow	Philips Healthcare, interventional X-ray Veenpluis 4-6 5684 PC Best The Netherlands [redacted]

APPENDIX III: USABILITY TESTING BACKGROUND

Usability testing refers to evaluating a device by testing it with representative users. Typically, during a test, participants will try to complete typical tasks while observers watch, listen and takes notes. The goal is to identify any usability problems, collect qualitative and quantitative data and determine the participant's satisfaction with the device. The intent is to improve the usability of devices to reduce use error.

During an usability test, observers will:

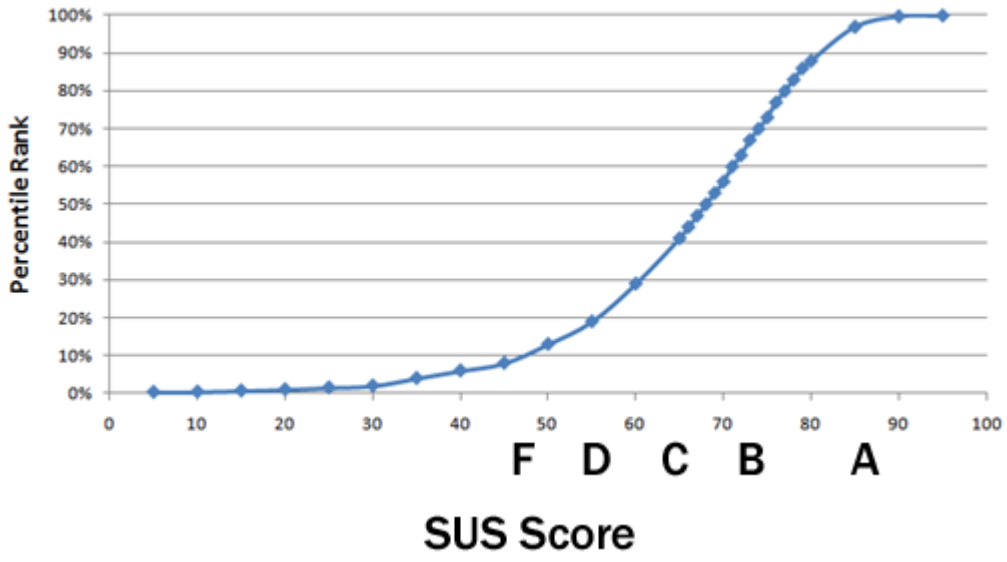
- Learn if participants are able to complete specified tasks (such as essential tasks and safety related tasks to measure effectiveness) successfully
- Identify how much effort does it takes to complete specified tasks (efficiency)
- Find out how satisfied participants are with the product
- Identify changes required to improve user performance and satisfaction
- Analyze the performance to see if it meets the usability objectives

System usability scale (SUS)

The SUS is a simple, ten-item attitude Likert scale giving a global view of subjective assessments of usability developed by Brooke, J[30,31,32,33]. The user needs to provide agreement or disagreement for the 10 statements. (See also Appendix IV: System usability scale) After the appearing of the SUS in literature and once part of the ISO standard ISO 9241 Part 11 it has become an industry standard and has been used for over 25 years to measure usability.

To interpret the SUS score, it is converted to a percentile rank through a process called normalizing. The graph below shows how the percentile ranks associate with SUS scores and letter grades. For example, a raw SUS score of a 74 converts to a percentile rank of 70%. A SUS score of 74 has higher perceived usability than 74% of all products tested. It can be interpreted as a grade of a B.

Analysis of 500 studies with SUS showed that the average SUS score is a 68. A SUS score above a 68 would be considered above average and anything below 68 is below average.[34]



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APPENDIX IV: SYSTEM USABILITY SCALE

Instruction: Please fill in this questionnaire, which asks you to indicate whether you agree or disagree with ten statements. You don't need to take a lot of time thinking about each question, just give your first impression. If you can't answer a particular question, please mark the center point.

Date of completion:	□□/□□□/□□□□ *Example: 05 / Jan / 2016*
Initials of person:	
Function:	□ Physician □ Technician
How many spine procedures do you perform on average per month?	_____Months
How many years of experience do you have with the Allura?	_____Years
How many interventions with Surgical Navigation did you approximately perform?	Total of :_____ procedures with Surgical Navigation
Age range (Years):	□ 20-39 □ 40-59 □ 60 and above

Please indicate how much you disagree or agree with the following statements:	**Strongly Disagree**				**Strongly Agree**
1. I think that I would like to use this system frequently.	1	2	3	4	5
2. I found the system unnecessarily complex.	1	2	3	4	5
3. I thought the system was easy to use.	1	2	3	4	5
4. I think that I would need the support of a technical person to be able to use this system.	1	2	3	4	5
5. I found the various functions in the system were well integrated.	1	2	3	4	5
6. I thought there was too much inconsistency in this system.	1	2	3	4	5
7. I imagine that most people would learn to use this system very quickly.	1	2	3	4	5
8. I found the system very awkward/cumbersome to use.	1	2	3	4	5
9. I felt very confident using the system.	1	2	3	4	5
10. I needed to learn a lot of things before I could get going with this system.	1	2	3	4	5

APPENDIX V: BACKGROUND INFORMATION PRIMARY OBJECTIVE

The classification system used in this study is as follows:

- grade 0 = breach 0 mm
- grade 1 = lumbar and thoracic < 2 mm, cervical <1 mm breach distance
- grade 2 = lumbar and thoracic 2-4 mm, cervical 1-2 mm breach distance
- grade 3 = lumbar and thoracic > 4 mm, cervical >2 mm breach distance

This classification system describes the distance of breach. This is measured according to an adapted version of the in literature reported classification method by Gerztbein. This classification system is used for lumbar and thoracic region and is for this study adapted to also include the distance of the breach for pedicles placed in the cervical area.

Furthermore the direction of perforation is interesting to measure (lateral or medial breach), since the consequences of the breach in a different direction might lead to different complications. Therefore additional information will be collected to report on the direction of perforation.

Additionally, the distance between the planned path and the longitudinal axis of the screw indicate how accurate the pedicle screw can be placed according to the planned path. When using the distance between planned path and longitudinal axis of the screw in smallest area of the pedicle (mm), one measures at the most critical point in the pedicle. When measuring the distance between screw tip of the screw and the planned target of screw (mm), this is measured at the somewhat less critical point at the point of the screw.