# Deliverable 7.6

# Investigator`s Brochure

| Dissemination | | |
|---|---|---|
| **Level** | **Type** | **Delivery Month** |
| ☐ Confidential (CO)<br>☐ Restricted (RE)<br>☒ Public (PU) | ☒ Report (R)<br>☐ Prototype (P)<br>☐ Other (O) | 24 |

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|---|---|
| **Deliverable** | D7.6 |
| **Milestone** | *MS9* |
| **Work Package Leader** | UKA-CTCA |
| **Task/Deliverable Leader** | UKA-CTCA |
| **Deliverable Due Date** | 31/10/2015 |
| **Date of Submission** | 02/11/2015 |
| **Version** | 1.1 |
| **Keywords** | Evaluation study, Instruction for study protocol |
| **Internal Report Review** | Done by management body |

| Version Control | | | |
|---|---|---|---|
| **Version** | **Date** | **Author (Name, Institution)** | **Comments** |
| **1.0** | 30.10.2015 | *Alexandra Greindl* | |
| **1.1** | 02.11.2015 | *Júlia Oliveira* | |
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1.X = 1st version circulating between the members / 2.X = 2nd version following comments of members / 3.X = 3rd final version

## Table of Contents

# 1 Introduction

Study planning requires comprehensive considerations on many aspects, starting with the definition of the scientific objectives, continuing with the fulfillment of ethical and legal requirements, the establishment of feasible and robust study specific work flows, the creation of valid electronic data capture procedure and statistical considerations regarding a proper analysis of results. All aspects must be consistant with one another and makes a study to a complex task.

The present Investigator`s Brochures (IB) for each study which are planned in RASimAs should be applied as instructions for the implementation of the respective study protocol on site. It will support particularly the study staff who did not participate in the progress of the project but who are assigned to support the study conduction on site. As a prerequisite for a consistent data collection it is important that the study staff become quickly familiar and skilled with all study structures. This can be ensured by providing IBs beside other appropriate formats for self-directed informing.

## 1.1 Context

After the second year of the project the development of the prototypes for simulation and for assistance of femoral nerve block procedures is well advanced and the possibilities as well as the limitations of the devices are clear-cut. Thus, it made it possible to define valid strategies for evaluation of the functionalities of the devices in controlled study experiments.

The study for evaluation of the simulator will take place within a medical healthcare setting and will involve medical graduates in specialist training in anaesthesia.

As the study for evaluation of the assistant system will include medical students within a non-clinical university setting.

## 1.2 Objectives

The objective of the present deliverable is to give a comprehensive overview and guidance to all aspects and work flows of each study to every person who is involved in conducting the study. The Investigator`s Brochure is partly overlapping with the study prorocols but goes beyond it. The IB document guides the study staff by indicating responsibilities, explaining study related procedures and tasks and by referring to corresponding documents with special attention to the data management and recording.

### 1.2.1 Deliverable description

As stated in the Description of Work, the deliverable that constitutes this plan is described as follows:

> ***D7.6 Investigator`s Brochure***
>
> *An Investigator`s Brochure based on the Technical File of the medical device will be prepared. The IB summarizes all information and instructions of critical importance for the investigator for the performance of a clinical trial.*

## 2 Applicable documents

**Annex I:** Investigator`s Brochure, Evaluation of the Simulator System

**Annex II:** Investigator`s Brochure, Evaluation of the Assistant System

# Investigator`s Brochure

**Research Project** RASimAs

**I. Study Title**

Evaluation of Regional Anaesthesia Simulator (RASim) System for self-directed Training of Novices in Regional Anaesthesia

**Study Protocol Version**

01

**Study Protocol Date**

tbd

**Study Code**

14-160

**Coordinating Investigator**

Dr Brian O`Donnell, MD

| | |
|---|---|
| **Document Version** | 01, First Version |
| **Document Date** | 2015-09-28 |
| **Author** | Alexandra Greindl |

This document contains confidential information. Any information concerning the clinical research activities of the RASimAs project which has not been specifically released to the general public should be treated confidentially.

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## Document History and Approval Page

The Investigator`s Brochure (IB) is a living document throughout the life cycle of a study. Therefore any changes or modifications made to the study protocol or any processes having an impact on the schedule of the study will also be covered within the IB. Changes will be tracked in the following modification history table.

| Version | Date | Affected Section(s) | Summary of Revisions Made |
|---|---|---|---|
| 01 | 2015-09-28 | --- | First version |
| | | | |
| | | | |

The IB is created, updated and provided by the data coordinating center. The undersigned have reviewed the IB and agree to scope, content and responsibilities. Draft versions do not need approval.

| Name | Function | Date | Signature |
|---|---|---|---|
| Prof Dr Thomas Deserno | Consortium`s Leader, Chief Data Manager | | |
| Dr Alexandra Greindl | Study Project Manager | | |
| Dr András Keszei | Statistician | | |

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## In-Scope

The present Investigator`s Brochure establishes an overall plan for the requirements of the study performance and data collection to ensure accuracy, integrity, consistency, reliability, and completeness of data. The IB refers to the study “Evaluation of the Regional Anaesthesia Simulator (RASim) System for self-directed Training of Novices in Regional Anaesthesia” which will be performed within the RASimAs project.

This IB is a guiding document to lead the Investigator and every other person involved in the data collection through the procedural structures that have been created and implemented for the data collection on site by the involved study staff.

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# 1 Introduction

The present Investigator`s Brochure is created as operational guide for the conduction of the RASimAs associated study. The IB provides an overview of the entire study related data collection procedures and other study-relevant tasks. It refers to corresponding documents and indicates the person in charge of the respective task.

Conduction of studies in compliance with the study protocol and all relevant ethical and legal requirements is a complex undertaking. The operational goal is to gather a robust and study protocol compliant data collection with a high reliability and a maximal reduced loss of information. In order to achieve this goal, critical aspects must be identified and taken into account during the planning of robust data collection procedures.

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**Table 1: Critical aspects of data collection in clinical studies.**

| Issue | Description & critical aspect(s) for study related data collection | Tools |
|---|---|---|
| **Multiprofessional teams** | Collection of study- specific endpoint and safety data as described in the protocol must be interpreted in terms of collection processes of each parameter group. Responsibilities with regards to process owner and process user.<br>**Critical aspects could be**: uncertainties regarding role and responsibilities to perform data collection tasks that could lead to loss of information; lack of knowledge regarding the study procedures | • Working plan with responsibility matrix<br>• Description of each collection process and creation of work aids (checklists, forms, templates, instructions etc.) which are filed in the ISF<br>• Introduction and training how to work with the ISF (kick-off meeting)<br>• Training of electronic data capture procedures |
| **Clinical routine care** | Study specific activities must be planned and implemented to avoid interference with processes of the routine care<br>**Critical aspects could be**: Change of the OR plan to perform FNB without combined general anaesthesia | • Establishment of regular project team meetings to clarify feasibility and implementation of study related project tasks into existing process structures of the clinical routine care existing at every site |
| **Infrastructure** | Feasibility for study performance due to infrastructural conditions must be checked for requirements to expand<br>**Critical aspects could be**: number of study subjects, number of FNB cases | • Identification of infrastructural requirements and creation of a checklist that defines the minimum requirements |
| **Staff** | Qualification<br>**Critical aspects could be**: lack of knowledge regarding GCP compliant data collection particularly with regards to data protection issues, data correction and general Good Clinical Practice | • Selection of study team members with a basic training that complies to their role in the study (Investigator, Study Nurse, Data Manager, Statistician etc.)<br>• Performance of training courses due to ethical/regulatory requirements and study specific issues |
| **Scientific equipment** | Study specific equipment<br>**Critical aspects could be**: usage of different equipment (US machines, needles, cameras for videotaping etc.) during the FNB performances could lead to a confounded data collection | • Identification of equipment and creation of material list(s)<br>• Implemented of logistical structures and procedures for order and shipment of study material |
| **Time resources** | Time planning<br>**Critical aspects could be**: if simulator sessions are not scheduled tightly for the trainees on site, the next study site cannot start to perform the study due to limited number of simulators; | • Creation of study work flow must be in compliance with the time resources of the study staff involved, if not further sites must be included as described as measure in the Quality Assurance Plan of the RASimAs project<br>• Simulator sessions tightly planned in blocks to release simulator device for a further session block at another site |

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| | | |
|---|---|---|
| **Budget** | Budget planning<br>**Critical aspects could be**: costs of RTD are not compliant with the project budget which is claimed for each partner | • All solutions must be put in the context of the claimed budget.<br>• The EU project manager of the RASimAs project will provide assistance for in questions of proper use of funds |
| **Project Timelines** | Project specific timelines<br>**Critical aspects could be**: recruiting rate is low | • Identification of reasons and introduction of appropriate measures |

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# 2 List of Abbreviations and Definition of Terms

| Abbreviation/Term | Definition |
|---|---|
| CRA | Clinical Research Associate (Monitor) |
| CRC | Clinical Research Coordinator (Study Nurse) |
| CRF | Case Report Form |
| CTC-A | Clinical Trial Center Aachen |
| DCC | Data Coordinating Center |
| Discrepancy | Data point that fails to pass a validation check |
| DM | Data Management |
| DMP | Data Management Plan |
| DMP | Data Management Plan |
| DMVP | Data Management & Validation Plan |
| eCRF | electronic Case Report Form |
| EDC | Electronic Data Capture |
| EOT | End of Trial |
| EOT | **E**nd **o**f **t**rial |
| FNB | Femoral Nerve Block |
| IB | Investigator`s Brochure |
| ICF | Informed Consent Form |
| ICH | International Declaration of Helsinki |
| ID | Identity |
| ISF | Investigator Site File |
| KU Leuven | Katholieke Universiteit Leuven |
| Multivariate Edit Check | An edit check (above and beyond a range check, valid check, or required criterion) on a variable or set of variables on the same CRF page (module) |
| OC | OpenClinica |
| RA | Regional Anaesthesia |
| RAAS | Regional Anaesthesia Assistant System |
| RWTH | Rheinische Westfälische Technische Hochschule |
| SD | Standard deviation |
| Sim | Simulator |

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| Abbreviation/Term | Definition |
|---|---|
| SOP | Standard Operation Procedure |
| Study Project Manager | Individual who manages the project at data coordinating center and takes over study team lead |
| TMF | Trial Master File |
| UCC | University College Cork |
| US | **u**ltra**s**ound |
| VPH | Virtual Physiological Human |
| VR | Virtual Reality |

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# 3 Dynamic References

Dynamic references are part of the data collection activities but not considered part of the IB. These documents are stored separately and annexed to this IB. The Document Owner is in charge of creation and update of the document. The Study Project Manager is in charge of filing all the documents in the appropriate file and of communicating any changes which might affect procedural and data recording issues.

**Table 2: Dynamic references applicable to the IB**

| Item | Content | Document Owner | Comment |
|---|---|---|---|
| Quality Assurance Plan | Overall quality management plan | Study Project Manager | Deliverable D7.1 |
| Data Management Plan | Data entry plan | Study Project Manager, Statistician | Deliverable D7.5 |
| SOPs and working instructions | List of documents | Study Project Manager | Filed in ISF and SMT by Study Project Manager |
| Trial Master File | Overall study file | Study Project Manager | Physically stored at the data coordinating center in Aachen |
| Investigator Site File (ISF) | Study site file<br>• Protocol<br>• ICFs<br>• Contact information<br>• SOPs<br>• Data entry forms, etc. | Study Project Manager, Monitor | Created for every site and stored at each site |
| SOP RASim guided simulator training | Application of the simulator device | Principal Investigators, Simulator Developers | Deliverable D6.1 |
| Instructions for videotaping | Instruction for videotaping during FNB procedure and video editing for upload to the eCRF | Task leader as described in the working plan | Study staff is instruction user |
| Instructions for video assessment | SOP for assessment of videos made during the FNBs performances | Task leader as described in the working plan | Training will take place during investigator`s and kick-off meetings |
| Logistics | Material list, instructions for order and shipment of material and equipment | Study Project Manager | |
| Training material | List containing description and access information of training material (training videos) | Study Project Manager, Monitor | |
| Working Plan | Identification of all study related tasks and persons in charge | Study Project Manager | Distributed to study team |

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This symbol can appear at the end of sections. It indicates corresponding dynamic documents to the sections below.

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# 4 Responsibilities

The responsibilities with regards to the data collection procedures are defined as indicated in the table below.

**Table 3: Distribution of responsibilities during data collection procedures.**

| Role | Description |
|---|---|
| Principal Investigator | Physician who is responsible for the data collection performed in compliance with the applicable ethical and legal requirements and the study protocol at the respective study site:<br>• Scientific advice<br>• Appropriate recruiting rate<br>• Informed consent of trainees, patients, medical staff<br>• Right for electronic signature for data entry approval<br>• Baseline training of study subjects<br>• Supervising FNB blocks<br>• Data entry/ query resolution |
| Sub-Investigator | Physician supporting PI in operational tasks:<br>• Informed consent of trainees, patients, medical staff<br>• Right for electronic signature for data entry approval<br>• Baseline training of study subjects<br>• Supervising FNB blocks<br>• Data entry/ query resolution |
| Clinical Research Coordinator/ Study Nurse | Any person who is member of the study team on site.<br>• Operational study assistance<br>• Data recording<br>• Data entry/ query resolution |
| Data Manager | Database programmer of the data coordinating center. The data manager is not a member of the RASimAs project team and act only upon the Study Project Manager`s instructions and requests.<br>• Database set up<br>• User account management<br>• Database lock |
| Study Project Manager | Manager provided by the data coordinating center.<br>• Management of the interfaces between all involved persons and parties<br>• Document management<br>• Project and quality management<br>• Definition of database requirements |
| Monitor | Clinical research associate provided by the data coordinating center.<br>• Kick-off meeting<br>• Site support for protocol compliant data collection<br>• Source data verification (SDV on site)<br>• Online monitoring<br>• Creation of queries |

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| Role | Description | | |
|---|---|---|---|
| FNB video Assessor | Independent physician blinded against group allocation of trainees and site performing the FNB<br>• Study standard guided assessment of the videotaped FNBs performed by the study subjects<br>• Data entry/ query resolution<br>• Right for electronic signature for data entry approval | | |
| Technical support | Technical support is provided threefold | | |
| | **SMT** support:<br>Electronic bug report function powered by Department of Medical Informatics, RWHT Aachen University Hospital | **eCRF** support:<br>Study project manager; EDC database powered by Department of Medical Informatics, RWHT Aachen University Hospital | **Simulator** support:<br>SenseGraphics will provide technical support by phone and on site by delegates |

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# 5 Study schedule

In the following, the study schedule is described by its most important characteristics. The responsibilities within tasks regarding the activities in study performance, data collection, study and data management are defined in each section.

- Study Protocol, latest version

## 5.1 Aim of the study

The aim of the study is to evaluate and compare ultrasound-guided regional anaesthesia skills in trainee anaesthetists trained with or without the RASim system.

## 5.2 Study duration

The planned study duration is from 01.02.2016 until 30.09.2016. For the single site the study duration may vary within this timeframe.

## 5.3 Study Population

In total 30 anaesthetics trainees without experience in performing loco-regional anaesthesia will be included in the study. The trainees will be allocated to the simulator training group and the control group equally. All sites will recruit study subjects in equal parts. The individual recruiting at the sites will be done in blocks and vary within this timeframe due to different availability of the simulator device at the site.

## 5.4 Participating Study Sites

**Table 4: Clinical study sites**

| Country | Site | Role | Principal Investigator |
|---|---|---|---|
| Belgium | Department of Anaesthesia<br>University Hospital Leuven | Recruiting site | Dr Steve Coppens, MD |
| Germany | Department of Anaesthesia<br>University Hospital Aachen | Recruiting site,<br>Data coordinating center | Dr Oliver Grottke, MD, PhD |
| Ireland | Department of Anaesthesia<br>University College Cork | Recruiting site,<br>Scientific coordinating center | Dr Brian O`Donnell, MD |

## 5.5 Ethical and legal requirements

The current study is not a clinical trial. No patients will be included. Additionally, no healthy volunteers will be recruited for any prospective interventional treatment that would fall under the regulation of the national drug or medical device act or the professional code of conduct for medical doctors. However, the study will be conducted in a healthcare setting but all FNB procedures will be carried out as it is normally done at the study sites in the context of FNB training. The current study will not influence the normal course of FNB.

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The study is a training study for physicians during their education in regional anaesthesia. Study participants will give their written informed consent before participating in the study procedures.

All regulations for data protection are applicable and will be ensured by the RASimAs consortium.

### 5.6 Study registration

The study will be registered at ClinicalTrials.gov prior to first subject in. The NCT number which will be received after successful registration procedure will be recorded in the Study Management Tool.

The Study Project Manager will be responsible to register the study project at ClinicalTrials.gov, to manage the update the database regarding the status of the study.

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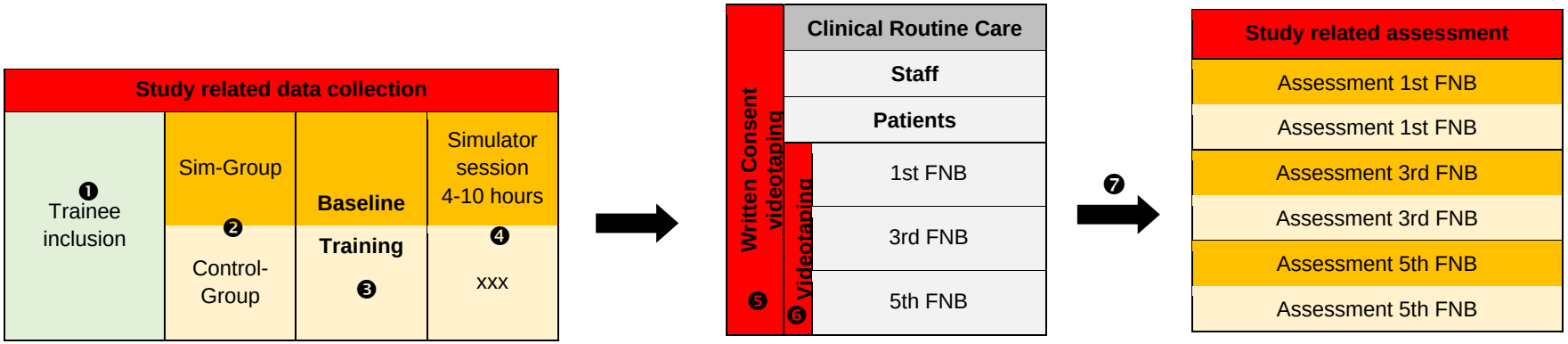
## 5.7 Flow Chart




❶: after written consent 30 trainees for regional anaesthesia in total will be enrolled to the study

❷: subjects will be allocated to one of the two study arms randomly

❸: all subjects receive an introduction to the field of RA and FNB by a standardized baseline training (theory, US imaging, needle guidance)

❹: subjects allocated to the Sim-group will perform self-directed simulator sessions within a limited timeframe

❺: for assessment of effects of previous simulator training, FNBs performed by study subjects during clinical routine care will be evaluated. Assessment will be done by independent experts and is based on videos made during the FNBs performed by each subject. To create, use and store study related image material it is mandatory to obtain written consent from the patients and the assisting medical staff.

❻: the first, third and fifth block performed by each subject will be videotaped

❼: videos will be uploaded to the eCRF and randomly allocated to the evaluating experts

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# 6 Data Collection, Recording and Management

Data recording takes place electronically by using the electronic data capture software *OpenClinica* that provides data entry in electronic case report forms (eCRFs). Due to procedural circumstances the eCRFs might not be intended for initial data entry. The Study Project Manager will create paper-based data entry work sheets for initial data entry. If paper-based documentation is done, the data entry person is obliged to label each single page with the subject ID and, after randomization, by using the random ID.

The study staff is in charge of transferring, entering and uploading all data which are collected at their study site and which are required for completion of the eCRFs.

The monitor is in charge of supporting the sites to collect the data according to the study protocol and all derived working instructions. Furthermore, the monitor is responsible to ensure that the data collection is in line with the defined data quality criteria.

The study project manager is responsible to support all study sites with the goal to ensure proper recruiting rates and introduce appropriate measures to keep objectives and the timelines.

- Data Management Plan

## 6.1 CTC-A Study Management Tool (SMT)

The SMT is a web-based electronic database for study management to provide all study relevant information and documents to each member of the involved study team.

Essential records in the SMT are:

- Reference numbers (Ethics, Study registration)
- Responsibilities & Roles of members of the study team
- Status of the study at the site
- Recruiting rate (automatically generated)
- Document sharing
- Comment fields for individual records by the user

Each person involved in the performance of the study will have an individual password protected access to the SMT. The user interface is available at:

http://ctc-a.rwth-aachen.de:8080/StudyManagement/

The study team have only access to the relevant data of their own study site. The SMT has a functional interface to an electronic randomization tool and the electronic data capture system.

The following table shows the distribution of the responsibilities regarding the application and maintenance of the study documentation within the SMT.

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**Table 5: Responsibilities in application and maintenance of the SMT**

| Role | Responsibility |
|---|---|
| Study staff (data entry person) | • Creating new study subjects and randomization of study subjects<br>• Upload of relevant documents for sharing<br>• Recording of essential activities in the status report section<br>• Access level: own (read & write access to data of own site, upload access) |
| Study Project Manager | • User account managment (creation, access level, password resets)<br>• Recording of reference numbers<br>• Update of study status<br>• Completeness of study documentation<br>• Access level: master |
| Department of Medical Informatics at the RWTH Aachen | • Technical support (Bug report management)<br>• Database and server management |

## 6.2 Data Collection & Source Data

All work sheets provided by the CTC-A as data coordinating center can be used for initial data entry and are defined as source data. Initial paper-based data entry must be transferred by the study staff except the paper-based entries for assessment of videos which must be transferred by each respective assessor.

- Applicable work sheets filed in the ISF

## 6.3 Baseline Records ❶

Trainees for regional anaesthesia will be screened according to the inclusion and exclusion criteria as defined in the study protocol. Potential study subjects will be included into the study only after obtaining written consent for participation into the study.

After inclusion into the study the subject will be added to the eCRF by an individual subject ID and electronic data entry is started for the subject. Data entry can be done section by section as soon as data are available.

Every site will maintain a subject identification log that assigns personal identifying data (name) to the subjects. This list will be stored at the study site and never be handed to other project partners not employed at the study site or third parties. Only the monitor is allowed to have an insight of all data collected study related at the sites to follow his duty to monitor the compliance of the data collection with all applicable requirements.

- Work sheets as filed in the ISF
- Informed consent form for trainees in its latest version

## 6.4 Pseudonymisation procedures

During the course of the study two different individuals codes will be generated for subject identification. This is required to collect data of the study subject in a pseudonymised manner to assure their rights of privacy.

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Subject ID:

After enrolment into the study the subject receives the subject ID. The study nurse will maintain a subject identification list only in the ISF. This list records personal identifying data and subject IDs. Only study staff on site and the monitor will have access to this list.

The subject ID has the following format: S[0]-[00]

- S[0]: the first alphanumeric part of the code identifies the study site, "S" is the abbreviation for "**S**imulator Study", "0" is replaced by the one-digit numeric code assigned to the site
- [00]: indicates the code of the subject as running numbering

### 6.5 Randomization of study subjects ❷

After inclusion the subject to the study, the subject will randomly allocated to one of the study arms. The data entry person will login to the SMT, select the study and applies the randomization tool as explained during data entry training sessions and described in the a training video which can be retrieved by the following link:

🗐 https://www.youtube.com/watch?v=GErVjn_mr0o

After randomization the data entry person receives the information of the study arm allocation and a unique randomization number is created automatically. This randomization number must be entered into the eCRF and every single page of paper-based source data.

The randomization number has the following format: [000]-RAND-[0000]

### 6.6 Baseline Training ❸

The field of regional anaesthesia and the performance of a femoral nerve block will be introduced to all subjects with an standardised baseline training according to the SOP. This training course will be held by each Principal Investigator prior to the start of simulator sessions.

🗐 SOP Baseline training for introduction of regional anaesthesia

### 6.7 Simulator Training ❹

SenseGraphics or a delegated and qualified person is in charge of the deployment of the simulator on site. Each study team will receive an introduction and training for application of the device on site.

Study subjects who are allocated to the simulator group have an obligation to participate in self-directed training sessions within a timeframe from 4 to 10 hours as maximum training experience in total.

The investigator will give an introduction of the application of the simulator to the study subjects prior to the start of simulator sessions. The on site study coordinator is responsible

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for tight coordination of subjects and training sessions. Assuming an equal recruitment over all participating study site at least five study subjects must be managed for simulator training.

The simulator software creates a user activity report to record the user activity in total. Each simulator user account is blocked after a total training time of 10.5 hours. The data entry person is responsible for uploading the user activity report to the eCRF as evidence for protocol compliant amount of simulator training. If a study subject fails to complete the required minimum duration of 4 hours simulator training the subject will be indicated as non-compliant but assessed and included in an Intention-to-treat analysis.

- Simulator deployment and training log (ISF) to be filled by SenseGraphics
- SOP RASim guided simulator training

### 6.8 Selection criteria for patients ❺

In order to reduce the risk of potential complications which could affect patient`s safety and success of block performance by the trainee, general health conditions and concomitant diseases are described in the study protocol that lead to defined selection criteria for patients that are eligible for the study subjects during their study participation.

Investigators and Clinical Research Coordinators will be responsible for selection of patients who are elective for FNB and meet all selection criteria

- Study Protocol in its latest version

### 6.9 Informed Consent involved parties ❺

Written consent must be obtained from the assisting medical staff and the patients who are scheduled for a femoral nerve block within the clinical routine care to obtain permission for videotaping, use and storage of image material that shows small parts of body regions that appear in a limited sight field during the FNB performance. The Investigator is responsible to obtain written informed consent.

All signed consent forms must be stored in its original version in the ISF or a study specific file.

For matters of traceability and with respect to data protection issues, the recording of the selection criteria of the patients will be done in a pseudynonymised manner.

The patient ID has the following format: S[0]-[00]-[0]

- S[0]: the first alphanumeric part of the code identifies the study site, “S” is the abbreviation for “**S**imulator Study”, “0” is replaced by the one-digit numeric code assigned to the site
- [00]: indicates the code of the subject as running numbering
- [0]: indicates the patient treated by the study subject as running numbering

- Informed consent forms for patients and medical staff in its latest version

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### 6.10 Videotaping of FNBs ❻

According to an SOP that describes the entire videotaping process including camera positioning, record time and video editing the first, third and fifth FNB performed by the trainee will be recorded for later assessment.

The study nurse will be trained to make the videos.

It is mandatory to obtain written consent from the patients and the assisting medical staff to produce, use and store image material showing parts of their body regions. The videos will not show any personal identifying body regions (faces).

All signed consent forms must be stored in the ISF or a study specific file in its original version.

- SOP Videotaping of FNB and instructions for video editing

### 6.11 Performance of Femoral Nerve Blocks

All study subjects regardless their group allocation will perform femoral nerve blocks during their regular clinical routine care and with patients who are scheduled for undergoing an FNB procedure within their regular routine care. The study subject will perform the nerve blocks under supervision of an experienced regional anaesthesiologist as it is the traditional accepted way to educate trainees in loco-regional anaesthesia. The 1st, 3rd, and 5th block performed by each study subject will be vidieotaped for the purposes of this study.

All sites will use the same ultrasound machines. The US machines which will be provided to the sites for free by an external company and will be limited to the study duration. The Principal Investigators and the Study Project Manager are in charge that the machines are put into service on time.

### 6.12 Assessment ❼

Multiple external assessors and experts from each study site will evaluate the FNB performance of the trainees independently. The videos will be allocated randomly to the assessors by the Statistician. Assessors will not be allocated to evaluate videos made at their own clinical site. For standardised assessment a validated questionnaire will be developed. The questionnaire contains the certain sequence of relevant procedural steps of an FNB procedure and in a second part a list that includes procedural errors that occur frequently during FNBs performed by novices. The assessor is in charge to evaluate if the trainee conducts the FNB in the correct sequence and performance of the given procedural steps and if errors which are indicated in the list occurred. The Coordinating Investigator will introduce the assessment tool to the assessors who will be practically trained by evaluating training videos prior to start of study related assessment.

- Data entry form for video assessment

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### 6.13 Data entry

The investigator(s) or designee(s) will be responsible for the data entry into the EDC system. The access to the EDC system is controlled by user name and password. Any change in the database is registered by means of an audit trail. The reason for accessing, user name, date and time, table name, old and new values and subject ID is recorded

### 6.14 Simulator Device Management

In total, two simulators will be available, which means that only two study sites can run the simulation sessions concurrently.

Initial deployment of the simulators will be in Leuven and in Cork, thus study start in Aachen is shifted until one device can be released from Leuven or Cork.

#### 6.14.1 Deployment & technical support

Initial deployment will be done by SenseGraphics or designee(s).

The Department for Medical Informatics will provide technical support for the sites in Aachen and Leuven to put the device into service if the device is swapped between Aachen and Leuven.

SenseGraphics will provide technical support for the site in Cork.

- Detailed contact information filed in the ISF

### 6.15 eCRF

The eCRFs are programmed in OpenClinica. This EDC system provides a web-based user interface and is available at:

http://openclinica2.rwth-aachen.de/openclinica/

Access rights correspond to the role which is assigned to the study team member. Regarding this roles, access can be distinguished for “Investigator”, “Clinical Research Coordinator”, “Monitor”, “Data Manager” and “Statistician”. Rights and responsibilities are described in Table 3.

Since the access rights of the EDC system cannot be cut down to single eCRF pages it was necessary to program the eCRF set for assessment of the videos separately from the eCRFs for data collection. With this it is possible to create a user interface which is exclusive for assessor with a status of an investigator in terms of access level.

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### 6.15.1 eCRF set for data collection on study sites

Data collection include all parameters except those which will be collected within the assessment of the FNB videos. The study staff is responsible to upload the videos of each study subject.

**Table 6: Access rights of users defined in OpenClinica for the data collection on site.**

| Role | Issue | Access right to data collection |
|---|---|---|
| Investigator | Data entry | ☒ yes ☐ no |
| | Query resolution | ☒ yes ☐ no |
| | Data entry approval | ☒ yes ☐ no |
| | Viewing rights own | ☒ yes ☐ no |
| | Viewing rights all sites | ☐ yes ☒ no |
| Clinical Research Coordinator/ Study Nurse | Data entry | ☒ yes ☐ no |
| | Query resolution | ☒ yes ☐ no |
| | Data entry approval | ☐ yes ☒ no |
| | Viewing rights own | ☒ yes ☐ no |
| | Viewing rights all sites | ☐ yes ☒ no |
| Monitor | Data entry | ☐ yes ☒ no |
| | Query *creation/follow up* | ☒ yes ☐ no |
| | Data entry approval | ☐ yes ☒ no |
| | Viewing rights own | ☒ yes ☐ no |
| | Viewing rights all sites | ☒ yes ☐ no |
| Assessor (Investigator) | Data entry | No Access |
| | Query resolution | |
| | Data approval | |
| | Viewing rights own | |
| | Viewing rights all sites | |
| Data Manager | Master access level | |
| Statistician | Creation of randomization scheme<br>Access to raw data after database lock | |

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### 6.15.2 eCRF set for independent assessment

To keep the assessors blinded regarding the group allocation of trainees and for reasons of data protection the assessor will have no access to the data collection eCRFs. The Statistician will create a random list to allocate the videos randomly to the assessors. According to this list the Statistician will provide the video links within the eCRF to each assessor.

**Table 7: Access rights of users defined in OpenClinica for independent assessment**

| Role | Issue | Access right to data collection |
|---|---|---|
| Investigator | Data entry | No Access |
| | Query resolution | |
| | Data entry approval | |
| | Viewing rights own | |
| | Viewing rights all sites | |
| Clinical Research Coordinator/ Study Nurse | Data entry | No Access |
| | Query resolution | |
| | Data entry approval | |
| | Viewing rights own | |
| | Viewing rights all sites | |
| Monitor | Data entry | ☐ yes ☒ no |
| | Query *creation/follow up* | ☒ yes ☐ no |
| | Data entry approval | ☐ yes ☒ no |
| | Viewing rights own | ☒ yes ☐ no |
| | Viewing rights all sites | ☒ yes ☐ no |
| Assessor | Data entry | ☒ yes ☐ no |
| | Query resolution | ☒ yes ☐ no |
| | Data approval | ☒ yes ☐ no |
| | Viewing rights own | ☒ yes ☒ no |
| | Viewing rights all sites | ☐ yes ☒ no |
| Data Manager | Master access level | |
| Statistician | Creation of randomization scheme<br>Access to raw data after database lock | |

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# 7 Training Study Performance

Study flow and study related procedures will be introduced to every study team on site during the study kick-off meeting by the Study Project Manager. During this meeting the ISF will be handed over to the team. The ISF includes all relevant information to conduct the study in compliance with the applicable internal and external standards and regulations.

The Clinical Research Coordinator will maintain a training log to record the training activities of the study staff.

The following table provides an overview of training programmes which will be conducted prior to complex and demanding study related procedures with the aim to keep the experimental error as low as possible due to intersubject variability.

**Table 8: Training programmes for study staff in the Simulator Study**

| Issue | Description | Trainer | Trainee |
|---|---|---|---|
| SMT training | Creation of new subjects<br>Application of the tool | Study Project Manager | Study team |
| Randomizer training | Randomization by the SMT guided randomizer tool | Study Project Manager | Study team |
| Data entry | Initial data entry, corrections of source data | Study Project Manager | Study team |
| eCRF training | Test data training, query management | Study Project Manager | Study team |
| Procedural study flows | Study protocol, efficient implementation of study related activities, SOPs, working instructions | Document owner | Study team |
| Data protection | Pseudonymization,<br>Transfer of data | Study Project Manager | Study team |
| Train the trainer | Simulator software application | SenseGraphics | Study team |
| | Baseline training | Coordinating Investigator | Investigators |
| | Supervision of trainees during FNB | Coordinating Investigator | Investigators |

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# 8 Monitoring

The data coordinating center will provide monitoring activities as quality assurance measure. Interim monitoring visits will take place on a regular basis according to a mutually agreed schedule.

During these visits, the monitor will check for completion of the entries on the eCRF/CRF; for compliance with the clinical study protocol, ICH-GCP principles, the Declaration of Helsinki, and legal requirements; for the integrity of the source data with the eCRF/ CRF entries; and for subject eligibility. Monitoring also will be aimed at detecting any misconduct or fraud.

The investigator and all staff will be expected to cooperate with the monitor by providing any missing information whenever possible. The investigator must be available to answer questions arising during regular monitoring visits. In addition, the investigator is required to:

- Have all data properly recorded in the eCRF and subject files prior to each monitoring visit
- Have the source documentation available at the monitoring visits.

# 9 Communication

The Study Project Manager is responsible for maintaining an effective communication flow over all sites. This will include regular newsletters to inform the teams about the overall recruiting rates and all information which is relevant to conduct the study.

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# Investigator`s Brochure

**Research Project** RASimAs

**II. Study Title**

Evaluation of the functionality of the Regional Anasthesia Assistant System (RAAS) as aid for US-image interpretation in the context of the Femoral Nerve Block (FNB)

**Study Protocol Version**

01

**Study Protocol Date**

tbd

**Study Code**

14-161

**Coordinating Investigator**

Dr Dr Oliver Grottke, MD, PhD

| | |
|---|---|
| **Document Version** | 01, First Version |
| **Document Date** | 2015-09-28 |
| **Author** | Alexandra Greindl |

This document contains confidential information. Any information concerning the clinical research activities of the RASimAs project which has not been specifically released to the general public should be treated confidentially.

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## Document History and Approval Page

The Investigator`s Brochure (IB) is a living document throughout the life cycle of a study. Therefore any changes or modifications made to the study protocol or any processes having an impact on the schedule of the study will also be covered within the IB. Changes will be tracked in the following modification history table.

| Version | Date | Affected Section(s) | Summary of Revisions Made |
|---|---|---|---|
| 01 | 2015-09-28 | --- | First version |
| | | | |
| | | | |

The IB is created, updated and provided by the data coordinating center. The undersigned have reviewed the IB and agree to scope, content and responsibilities. Draft versions do not need approval.

| Name | Function | Date | Signature |
|---|---|---|---|
| Prof Dr Thomas Deserno | Consortium`s Leader,<br>Chief Data Manager | | |
| Dr Alexandra Greindl | Study Project Manager | | |
| Dr András Keszei | Statistician | | |

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## In-Scope

The present Investigator`s Brochure establishes an overall plan for the requirements of the study performance and data collection to ensure accuracy, integrity, consistency, reliability, and completeness of data. The IB refers to the study “Evaluation of the functionality of the Regional Anasthesia Assistant System (RAAS) as aid for US-image interpretation in the context of the Femoral Nerve Block (FNB)” which will be performed within the RASimAs project.

This IB is a guiding document to lead the Investigator and every other person involved in the data collection through the procedural structures that have been created and implemented for the data collection on site by the involved study staff.

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# Table of Content



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# 1 Introduction

The present Investigator`s Brochure serves as operational guide for the conduction of the RASimAs associated study. The IB provides an overview of the entire study related data collection procedures and other study-relevant tasks. It refers to corresponding documents and indicates the person in charge of the respective task.

Conduction of studies in compliance with the study protocol and all relevant ethical and legal requirements is a complex undertaking. The operational goal is to gather a robust and study protocol compliant data collection with a high reliability and a maximal reduced loss of information. In order to achieve this goal, critical aspects must be identified and taken into account during the planning of robust data collection procedures.

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**Table 1: Critical aspects of data collection in clinical studies.**

| Issue | Description & critical aspect(s) for study related data collection | Tools |
|---|---|---|
| **Multiprofessional teams** | Collection of study- specific endpoint and safety data as described in the protocol must be interpreted in terms of collection processes of each parameter group. Responsibilities with regards to process owner and process user.<br>**Critical aspects could be**: uncertainties regarding role and responsibilities to perform data collection tasks that could lead to loss of information; lack of knowledge regarding the study procedures | • Working plan with responsibility matrix<br>• Description of each collection process and creation of work aids (checklists, forms, templates, instructions etc.) which are filed in the ISF<br>• Introduction and training how to work with the ISF (kick-off meeting)<br>• Training of electronic data capture procedures |
| **Clinical routine care** | The study has no interface to the clinical routine care.<br>**Critical aspects could be**: not applicable | --- |
| **Infrastructure** | Feasibility for study performance due to infrastructural conditions must be checked for requirements to expand<br>**Critical aspects could be**: number of study subjects | • Every participating study site confirmed to have more than 200 medical students |
| **Staff** | Qualification<br>**Critical aspects could be**: lack of knowledge regarding GCP compliant data collection particularly with regards to data protection issues, data correction and general Good Clinical Practice | • Selection of study team members with a basic training that complies to their role in the study (Investigator, Study Nurse, Data Manager, Statistician etc.)<br>• Performance of training courses due to ethical/regulatory requirements and study specific issues |
| **Scientific equipment** | Study specific equipment<br>**Critical aspects could be**: usage of different equipment (US machines etc.) during the FNB performances could lead to a confounded data collection | • Identification of equipment and creation of material list(s)<br>• Implemented of logistical structures and procedures for order and shipment of study material |
| **Time resources** | **Critical aspects could be**: no critical timeline issues could be identified for the conduction of the assistant trial; low recruiting rate is not expected | --- |
| **Budget** | Budget planning<br>**Critical aspects could be**: costs of RTD are not compliant with the project budget which is claimed for each partner | • All solutions must be put in the context of the claimed budget.<br>• The EU project manager of the RASimAs project will provide assistance for in questions of proper use of funds |
| **Project Timelines** | Efforts for planned concept of study conduction are feasible with regards to the project timelines<br>**Critical aspects could be**: not applicable | --- |

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# 2 List of Abbreviations and Definition of Terms

| Abbreviation/Term | Definition |
|---|---|
| CRA | Clinical Research Associate (Monitor) |
| CRC | Clinical Research Coordinator (Study Nurse) |
| CRF | Case Report Form |
| CTC-A | Clinical Trial Center Aachen |
| DCC | Data Coordinating Center |
| Discrepancy | Data point that fails to pass a validation check |
| DM | Data Management |
| DMP | Data Management Plan |
| DMP | Data Management Plan |
| DMVP | Data Management & Validation Plan |
| eCRF | electronic Case Report Form |
| EDC | Electronic Data Capture |
| EOT | End of Trial |
| EOT | **E**nd **o**f **t**rial |
| FNB | Femoral Nerve Block |
| IB | Investigator`s Brochure |
| ICF | Informed Consent Form |
| ICH | International Declaration of Helsinki |
| ID | Identity |
| ISF | Investigator Site File |
| KU Leuven | Katholieke Universiteit Leuven |
| Multivariate Edit Check | An edit check (above and beyond a range check, valid check, or required criterion) on a variable or set of variables on the same CRF page (module) |
| OC | OpenClinica |
| RA | Regional Anaesthesia |
| RAAS | Regional Anaesthesia Assistant System |
| RWTH | Rheinische Westfälische Technische Hochschule |
| SD | Standard deviation |
| Sim | Simulator |
| SOP | Standard Operation Procedure |

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| Abbreviation/Term | Definition |
|---|---|
| Study Project Manager | Individual who manages the project at data coordinating center and takes over study team lead |
| TMF | Trial Master File |
| UCC | University College Cork |
| US | **u**ltra**s**ound |
| VPH | Virtual Physiological Human |
| VR | Virtual Reality |

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# 3 Dynamic References

Dynamic references are part of the data collection activities but not considered part of the IB. These documents are stored separately and annexed to this IB. The Document Owner is in charge of creation and update of the document. The Study Project Manager is in charge of filing all the documents in the appropriate file and of communicating any changes which might affect procedural and data recording issues.

**Table 2: Dynamic references applicable to the IB**

| Item | Content | Document Owner | Comment |
|---|---|---|---|
| Quality Assurance Plan | Overall quality management plan | Study Project Manager | Deliverable D7.1 |
| Data Management Plan | Data entry plan | Study Project Manager, Statistician | Deliverable D7.5 |
| SOPs and working instructions | List of documents | Study Project Manager | Filed in ISF and SMT by Study Project Manager |
| Trial Master File | Overall study file | Study Project Manager | Physically stored at the data coordinating center in Aachen |
| Investigator Site File (ISF) | Study site file<br>• Protocol<br>• ICFs<br>• Contact information<br>• SOPs<br>• Data entry forms, etc. | Study Project Manager, Monitor | Created for every site and stored at each site |
| SOP RAAs application | Application of the assistant device | Principal Investigators, Assistant Developers | Deliverable D6.1 |
| Instructions for annotation | Instruction for annotation of the US images by the medical students using Trackball | Task leader as described in the working plan | |
| Instructions for image assessment | SOP for assessment of images annotated by the medical students | Task leader as described in the working plan | Training will take place during investigator`s and kick-off meetings |
| Logistics | Material list, instructions for order and shipment of material and equipment | Study Project Manager | |
| Training material | List containing description and access information of training material | Study Project Manager, Monitor | |
| Working Plan | Identification of all study related tasks and persons in charge | Study Project Manager | Distributed to study team |

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This symbol can appear at the end of each section. It indicates corresponding dynamic documents to the sections below.

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# 4 Responsibilities

The responsibilities with regards to the data collection procedures are defined as indicated in the table below.

**Table 3: Distribution of responsibilities during data collection procedures.**

| Role | Description |
|---|---|
| Principal Investigator | Physician who is responsible for the data collection performed in compliance with the applicable ethical and legal requirements and the study protocol at the respective study site:<br>• Scientific advice<br>• Appropriate recruiting rate<br>• Informed consent of medical students<br>• Right for electronic signature for data entry approval<br>• Data entry/ query resolution<br>• Assessment of US images anntotated by the students<br>• Evaluation of assistant validity |
| Sub-Investigator | Physician supporting PI in operational tasks:<br>• Informed consent of medical students<br>• Data entry/ query resolution<br>• Assessment of US images anntotated by the students |
| Clinical Research Coordinator/ Study Nurse | Any person who is member of the study team on site.<br>• Operational study assistance (Management of live scans)<br>• Data recording<br>• Data entry/ query resolution |
| Data Manager | Database programmer of the data coordinating center. The data manager is not a member of the RASimAs project team and act only upon the Study Project Manager`s instructions and requests.<br>• Database set up<br>• User account management<br>• Database lock |
| Study Project Manager | Manager provided by the data coordinating center.<br>• Management of the interfaces between all involved persons and parties<br>• Document management<br>• Project and quality management<br>• Definition of database requirements |
| Monitor | Clinical research associate provided by the data coordinating center.<br>• Kick-off meeting<br>• Site support for protocol compliant data collection<br>• Source data verification (SDV on site)<br>• Online monitoring<br>• Creation of queries |

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| Role | Description | | |
|---|---|---|---|
| Technical support | Technical support is provided threefold | | |
| | **SMT** support:<br>Electronic bug report function powered by Department of Medical Informatics, RWHT Aachen University Hospital | **eCRF** support:<br>Study project manager; EDC database powered by Department of Medical Informatics, RWTH Aachen University Hospital | **Assistant** support:<br>Sintef will provide technical support by phone and on site by delegates |

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# 5 Study schedule

In the following, the study schedule is described by its most important characteristics. The responsibilities within tasks regarding the activities in study performance, data collection, study and data management are defined in each section.

- Study Protocol, latest version

## 5.1 Aim of the study

The aim of the study is to evaluate the functionality of the RAA system as an aid for interpretation of US images in the context of regional anaesthesia.

The investigation will clarify if doctors in training behave more like experts regarding the identification of FNB relevant anatomical structures by US scanning when guided by the assistant system compared to those who are not supported by additional information.

## 5.2 Study duration

The study start will be as soon as the prototype is available or on 1st of April at the latest. End of study will be by the end of

## 5.3 Study Population

In total 40 medical students after finishing their regular training in anatomy will be included in the study. The students will be allocated randomly to the assistant or to the control group in equal parts. One medical student will volunteer as model for live scanning

## 5.4 Participating Study Sites

**Table 4: Clinical study sites**

| Country | Site | Role | Principal Investigator |
|---|---|---|---|
| Belgium | Department of Anaesthesia<br>University Hospital Leuven | Recruiting site | Dr Steve Coppens, MD |
| Germany | Department of Anaesthesia<br>University Hospital Aachen | Recruiting site,<br>Data coordinating center | Dr Oliver Grottke, MD, PhD |
| Ireland | Department of Anaesthesia<br>University College Cork | Recruiting site,<br>Scientific coordinating center | Dr Brian O`Donnell, MD |

## 5.5 Ethical and legal requirements

The current study is not a clinical trial. No patients will be included. Additionally, no healthy volunteers will be recruited for any prospective interventional treatment that would fall under the regulation of the national drug or medical device act or the professional code of conduct for medical doctors. The study is a training study for doctors in training and for the evaluation of the validity of assistant prototype during their education in regional anaesthesia. Study

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participants will give their written informed consent before participating in the study procedures.

All regulations for data protection are applicable and will be ensured by the RASimAs consortium.

### 5.6 Study registration

The study will be registered at ClinicalTrials.gov prior to first subject in. The NCT number which will be received after successful registration procedure will be recorded in the Study Management Tool.

The Study Project Manager will be responsible to register the study project at ClinicalTrials.gov, to manage the update the database regarding the status of the study.

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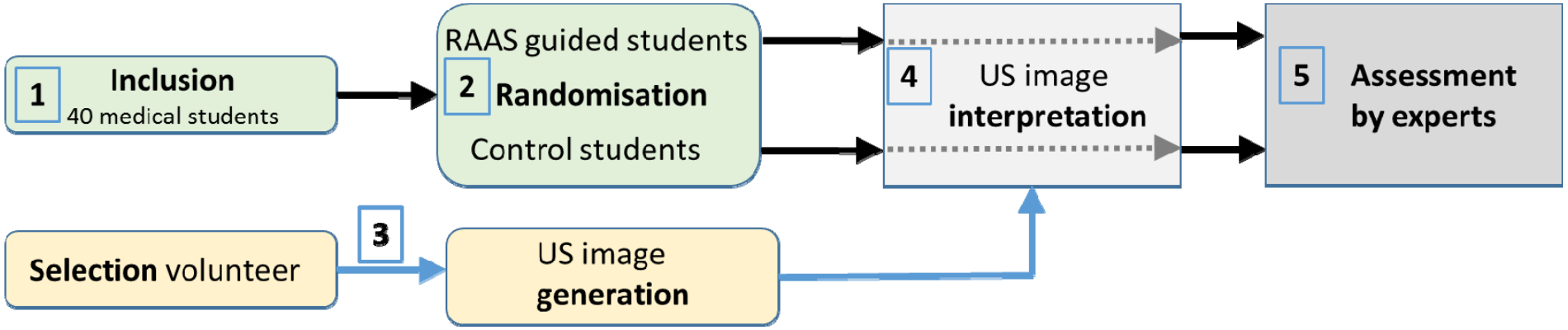
## 5.7 Flow Chart




❶: 40 medical students who have finished their regular training in anatomy will be included to the study.

❷: Students are allocated randomly and in equal parts to the assistant or the control group.

❸: One medical student (BMI < 35) at each site will volunteer for live scans by the study subjects. The study subjects will perform US live scans of the groin region in a self-directed manner. Subjects allocated to the assistant group will be guided by the assistant system to identify femoral nerve and artery. Subjects of the control group will perform the US live scan without any additional information.

❹: The participants in each group are asked to annotate the 'best' picture they obtained using the track ball volume analysis function.

❺: These images will then be assessed by blinded reviewers who will be asked to two questions:
1. Does the image obtained by the study subject contain the femoral artery and femoral nerve?
2. Did the study subject correctly identify the boundaries of the femoral nerve?
Each interpretation will be a data point in the analysis of group differences.

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# 6 Data Collection, Recording and Management

Data recording takes place electronically by using the electronic data capture software *OpenClinica* that provides data entry in electronic case report forms (eCRFs). Due to procedural circumstances the eCRFs might not be intended for initial data entry. The Study Project Manager will create paper-based data entry work sheets for initial data entry. If paper-based documentation is done, the data entry person is obliged to label each single page with the subject ID and, after randomization, by using the random ID.

The study staff is in charge of transferring, entering and uploading all data which are collected at their study site and which are required for completion of the eCRFs.

The monitor is in charge of supporting the sites to collect the data according to the study protocol and all derived working instructions. Furthermore, the monitor is responsible to ensure that the data collection is in line with the defined data quality criteria.

The study project manager is responsible to support all study sites with the goal to ensure proper recruiting rates and introduce appropriate measures to keep objectives and the timelines.

- Data Management Plan

## 6.1 CTC-A Study Management Tool (SMT)

The SMT is a web-based electronic database for study management to provide all study relevant information and documents to each member of the involved study team.

Essential records in the SMT are:

- Reference numbers (Ethics, Study registration)
- Responsibilities & Roles of members of the study team
- Status of the study at the site
- Recruiting rate (automatically generated)
- Document sharing
- Comment fields for individual records by the user

Each person involved in the performance of the study will have an individual password protected access to the SMT. The user interface is available at:

http://ctc-a.rwth-aachen.de:8080/StudyManagement/

The study team have only access to the relevant data of their own study site. The SMT has a functional interface to an electronic randomization tool and the electronic data capture system.

The following table shows the distribution of the responsibilities regarding the application and maintenance of the study documentation within the SMT.

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**Table 5: Responsibilities in application and maintenance of the SMT**

| Role | Responsibility |
|---|---|
| Study staff (data entry person) | • Creating new study subjects and randomization of study subjects<br>• Upload of relevant documents for sharing<br>• Recording of essential activities in the status report section<br>• Access level: own (read & write access to data of own site, upload access) |
| Study Project Manager | • User account managment (creation, access level, password resets)<br>• Recording of reference numbers<br>• Update of study status<br>• Completeness of study documentation<br>• Access level: master |
| Department of Medical Informatics at the RWTH Aachen | • Technical support (Bug report management)<br>• Database and server management |

## 6.2 Data Collection & Source Data

All work sheets provided by the CTC-A as data coordinating center can be used for initial data entry and are defined as source data. Initial paper-based data entry must be transferred by the study staff except the paper-based entries for assessment of videos which must be transferred by each respective assessor.

- Applicable work sheets filed in the ISF

## 6.3 Inclusion: Baseline Records ❶

Medical students will be screened according to the inclusion and exclusion criteria as defined in the study protocol. Potential study subjects will be included into the study only after obtaining written consent for participation into the study.

After inclusion into the study the subject will be added to the eCRF by an individual subject ID and electronic data entry is started for the subject. Data entry can be done section by section as soon as data are available.

Every site will maintain a subject identification log that assigns personal identifying data (name) to the subjects. This list will be stored at the study site and never be handed over to other project partners who are not employed at the study site (third parties). Only the monitor is allowed to have an insight of all data collected study related at the sites to follow his duty to monitor the compliance of the data collection with all applicable requirements.

- Work sheets as filed in the ISF
- Informed consent form for medical students in its latest version

## 6.4 Pseudonymisation procedures

During the course of the study two different individuals codes will be generated for subject identification. This is required to collect data of the study subject in a pseudonymised manner to assure their rights of privacy.

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Subject ID:

After enrolment into the study the subject receives the subject ID. The study nurse will maintain a subject identification list only in the ISF. This list records personal identifying data and subject IDs. Only study staff on site and the monitor will have access to this list.

The subject ID has the following format: A[0]-[00]

- A[0]: the first alphanumeric part of the code identifies the study site, "S" is the abbreviation for "**A**ssistant Study", "0" is replaced by the one-digit numeric code assigned to the site
- [00]: indicates the code of the subject as running numbering

### 6.5 Randomization of study subjects ❷

After inclusion the subject to the study, the subject will randomly allocated to one of the study arms. The data entry person will login to the SMT, select the study and applies the randomization tool as explained during data entry training sessions and described in the a training video which can be retrieved by the following link:

🗐 https://www.youtube.com/watch?v=GErVjn_mr0o

After randomization the data entry person receives the information of the study arm allocation and a unique randomization number is created automatically. This randomization number must be entered into the eCRF and every single page of paper-based source data.

The randomization number has the following format: [000]-RAND-[0000]

### 6.6 US image generation ❸

One medical student at each site will declare consent to provide themselves for US live scans of their groin region.

The live scan sessions are possible to be conducted within 3 days. The Clinical Research Coordinator is in charge to provide technical assistance for the application of the US machine and for the management of the study participants.

The Clinical Research Coordinator will pseudonymise the US image by labelling with the Random ID of each participate and upload it to the eCRF.

### 6.7 Assistant system

The project partners from Sintef or a delegated and qualified person are in charge of the deployment of the assistant on site. Each study team will receive an introduction and training for application of the device on site.

The investigator will give an introduction of the application of the assistant system to the study subjects prior to the start of US live scans.

🗐 Assistant deployment and training log (ISF) to be filled by Sintef

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- SOP RAAS guided application

### 6.8 US image interpretation/ annotation ❹

The students will be trained by the investigator in using the track ball volume analysis function to annotate femoral nerve and artery. They will be not assisted by a supervisor during the US scans and will identify anatomical structures based on own knowledge and information provided by the assistant.

### 6.9 Assessment ❺

Experts from each study site will evaluate the annotations of the US image independently. The images will be allocated randomly to the assessors by the Statistician. Assessors will not be allocated to evaluate US images made at their own clinical site.

According to the secondary objectives as defined in the study protocol. The assessors will evaluate the validity of the assistant system.

- Data entry form for US image assessment
- Study protocol

### 6.10 Data entry

The investigator(s) or designee(s) will be responsible for the data entry into the EDC system. The access to the EDC system is controlled by user name and password. Any change in the database is registered by means of an audit trail. The reason for accessing, user name, date and time, table name, old and new values and subject ID is recorded.

### 6.11 Assistant Device Management

In total, two assistant systems will be available.

Initial deployment of the systems will be in Leuven and in Cork, thus study start in Aachen is shifted until one device can be released from Leuven or Cork.

#### 6.11.1 Deployment & technical support

Initial deployment will be done by Sintef or designee(s).

The Department for Medical Informatics will provide technical support for the sites in Aachen and Leuven to put the device into service if the device is swapped between Aachen and Leuven.

Sintef will provide technical support for the site in Cork.

- Detailed contact information filed in the ISF

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### 6.12 eCRF

The eCRFs are programmed in OpenClinica. This EDC system provides a web-based user interface and is available at:

http://openclinica2.rwth-aachen.de/openclinica/

Access rights correspond to the role which is assigned to the study team member. Regarding this roles, access can be distinguished for “Investigator”, “Clinical Research Coordinator”, “Monitor”, “Data Manager” and “Statistician”. Rights and responsibilities are described in Table 3.

Since the access rights of the EDC system cannot be cut down to single eCRF pages it was necessary to program the eCRF set for assessment of the US images separately from the eCRFs for data collection. With this it is possible to create a user interface which is exclusive for assessor with a status of an investigator in terms of access level.

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### 6.12.1 eCRF set for data collection on study sites

Data collection include all parameters except those which will be collected within the assessment of the FNB videos. The study staff is responsible to upload the videos of each study subject.

**Table 6: Access rights of users defined in OpenClinica for the data collection on site.**

| Role | Issue | Access right to data collection |
|---|---|---|
| Investigator | Data entry | ☒ yes ☐ no |
| | Query resolution | ☒ yes ☐ no |
| | Data entry approval | ☒ yes ☐ no |
| | Viewing rights own | ☒ yes ☐ no |
| | Viewing rights all sites | ☐ yes ☒ no |
| Clinical Research Coordinator/ Study Nurse | Data entry | ☒ yes ☐ no |
| | Query resolution | ☒ yes ☐ no |
| | Data entry approval | ☐ yes ☒ no |
| | Viewing rights own | ☒ yes ☐ no |
| | Viewing rights all sites | ☐ yes ☒ no |
| Monitor | Data entry | ☐ yes ☒ no |
| | Query *creation/follow up* | ☒ yes ☐ no |
| | Data entry approval | ☐ yes ☒ no |
| | Viewing rights own | ☒ yes ☐ no |
| | Viewing rights all sites | ☒ yes ☐ no |
| Assessor (Investigator) | Data entry | No Access |
| | Query resolution | |
| | Data approval | |
| | Viewing rights own | |
| | Viewing rights all sites | |
| Data Manager | Master access level | |
| Statistician | Creation of randomization scheme<br>Access to raw data after database lock | |

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### 6.12.2 eCRF set for independent assessment

To keep the assessors blinded regarding the group allocation of trainees and for reasons of data protection the assessor will have no access to the data collection eCRFs. The Statistician will create a random list to allocate the videos randomly to the assessors. According to this list the Statistician will provide the video links within the eCRF to each assessor.

**Table 7: Access rights of users defined in OpenClinica for independent assessment**

| Role | Issue | Access right to data collection |
|---|---|---|
| Investigator | Data entry | No Access |
| | Query resolution | |
| | Data entry approval | |
| | Viewing rights own | |
| | Viewing rights all sites | |
| Clinical Research Coordinator/ Study Nurse | Data entry | No Access |
| | Query resolution | |
| | Data entry approval | |
| | Viewing rights own | |
| | Viewing rights all sites | |
| Monitor | Data entry | ☐ yes ☒ no |
| | Query *creation/follow up* | ☒ yes ☐ no |
| | Data entry approval | ☐ yes ☒ no |
| | Viewing rights own | ☒ yes ☐ no |
| | Viewing rights all sites | ☒ yes ☐ no |
| Assessor | Data entry | ☒ yes ☐ no |
| | Query resolution | ☒ yes ☐ no |
| | Data approval | ☒ yes ☐ no |
| | Viewing rights own | ☒ yes ☒ no |
| | Viewing rights all sites | ☐ yes ☒ no |
| Data Manager | Master access level | |
| Statistician | Creation of randomization scheme<br>Access to raw data after database lock | |

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# 7 Training Study Performance

Study flow and study related procedures will be introduced to every study team on site during the study kick-off meeting by the Study Project Manager. During this meeting the ISF will be handed over to the team. The ISF includes all relevant information to conduct the study in compliance with the applicable internal and external standards and regulations.

The Clinical Research Coordinator will maintain a training log to record the training activities of the study staff.

The following table provides an overview of training programmes which will be conducted prior to complex and demanding study related procedures with the aim to keep the experimental error as low as possible due to intersubject variability.

**Table 8: Training programmes for study staff in the Assistant Study**

| Issue | Description | Trainer | Trainee |
|---|---|---|---|
| SMT training | Creation of new subjects<br>Application of the tool | Study Project Manager | Study team |
| Randomizer training | Randomization by the SMT guided randomizer tool | Study Project Manager | Study team |
| Data entry | Initial data entry, corrections of source data | Study Project Manager | Study team |
| eCRF training | Test data training, query management | Study Project Manager | Study team |
| Procedural study flows | Study protocol, efficient implementation of study related activities, SOPs, working instructions | Document owner | Study team |
| Data protection | Pseudonymization,<br>Transfer of data | Study Project Manager | Study team |
| Train the trainer | Assistant software application | Sintef | Study team |
| | Assessment training | Coordinating Investigator | Investigators |

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# 8 Monitoring

The data coordinating center will provide monitoring activities as quality assurance measure. Interim monitoring visits will take place on a regular basis according to a mutually agreed schedule.

During these visits, the monitor will check for completion of the entries on the eCRF/CRF; for compliance with the clinical study protocol, ICH-GCP principles, the Declaration of Helsinki, and legal requirements; for the integrity of the source data with the eCRF/ CRF entries; and for subject eligibility. Monitoring also will be aimed at detecting any misconduct or fraud.

The investigator and all staff will be expected to cooperate with the monitor by providing any missing information whenever possible. The investigator must be available to answer questions arising during regular monitoring visits. In addition, the investigator is required to:

- Have all data properly recorded in the eCRF and subject files prior to each monitoring visit
- Have the source documentation available at the monitoring visits.

# 9 Communication

The Study Project Manager is responsible for maintaining an effective communication flow over all sites. This will include regular newsletters to inform the teams about the overall recruiting rates and all information which is relevant to conduct the study.

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