USZ Universitäts Spital Zürich

Clinical Study Protocol

Usefulness of Deep-Learning Image Reconstruction for Cardiac Computed Tomography Angiography - a Prospective, Non-randomized Observational Trial DLIR in CCTA

Study Type:	Intervention with CE approved Medical Device (IMD)
Study Categorisation:	Clinical Trial with IMD Category A
Study Registration:	This study will be registered in the Swiss Federal Complementary Database ("Portal") and in the international trial registry ClinicalTrials.gov (clinicaltrials.gov)
Study Identifier:	DLIR in CCTA
Sponsor, Sponsor-Investigator or Principal Investigator:	PD Dr. rned. Ronny Ralf Büchel Address: University Hospital Zurich Nuklearmedizin NUK C 42 Rämistrasse 100, 8091 Zürich Email: ronny.buechel@usz.ch Tel: 044 255 10 59 (IIT: Sponsor and Project Leader is the same person)
Investigational Product:	Deep-learning image reconstruction from GE Healthcare
Protocol Version and Date:	1.1

Signature Page

Study number	2019-00533
Study Title	Usefulness of Deep-Learning Image Reconstruction for Cardiac Computed Tomography Angiography - a Prospective, Non-randomized Observational Trial

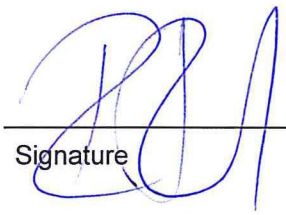
The Sponsor-Investigator and trial statistician have approved the protocol version [1.1 (dated 23.04.2019)], and confirm hereby to conduct the study according to the protocol, current version of the World Medical Association Declaration of Helsinki, ICH-GCP guidelines or ISO 14155 norm if applicable and the local legally applicable requirements.

Sponsor-Investigator:

PD Dr. med. Ronny R. Buechel

Zurich, 23.4.19

Place/Date



Signature

Local Principal Investigator at study site:

I have read and understood this trial protocol and agree to conduct the trial as set out in this study protocol, the current version of the World Medical Association Declaration of Helsinki, ICH-GCP guidelines or ISO 14155 norm and the local legally applicable requirements.

Site	University Hospital Zurich Nuklearmedizin NUK C 42 Rämistrasse 100, 8091 Zürich
Principal investigator	PD Dr. med. Ronny R. Buechel

Zurich, 23.4.19

Place/Date

Signature

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STUDY SYNOPSIS

Provide a structured synopsis containing all important information, preferably in tabular view:

Sponsor / Sponsor-Investigator	PD Dr. med. Ronny R. Buechel
Study Title:	Usefulness of Deep-Learning Image Reconstruction for Cardiac Computed Tomography Angiography - a Prospective, Non-randomized Observational Trial
Short Title / Study ID:	DLIR in CCTA / not yet available
Protocol Version and Date:	1.1 / 23.04.2019
Trial registration:	The study will be registered in the Swiss Federal Complementary Database ("Portal") and in the international trial registry ClinicalTrials.gov (clinicaltrials.gov)
Study category and Rationale	Clinical study with IMD Category A
Clinical Phase:	Phase of development: CE-marked, pre-commercial use
Background and Rationale:	Cardiac CT allows the assessment of coronary artery disease by ionising radiation. Although radiation exposure was significantly reduced in recent years, further technological refinements with artificial intelligence (deep-learning image reconstruction, DLIR) suggest improved post-processing of images with reduction of image noise.
Objective(s):	The present study assesses the impact of a DLIR algorithm on image noise, image contrast, image quality and evaluation of coronary plaques and lesion severity
Outcome(s):	- Subjective image quality obtained from the experimental intervention with the control intervention - Agreement of signal, noise, signal-to-noise ratio and contrast-to-noise ratio - Comparison of dose-length products and radiation exposure in mSv - Impact on assessment of coronary plaques and lesion severity - Applicability and performance of established software (e.g. for quantitative plaque analysis, for calculation of endothelial shear stress or CTFFR) in images reconstructed with DLIR - The results of further diagnostic tests (e.g. invasive coronary angiography, myocardial perfusion imaging) that are triggered by the clinical coronary CT scan will be compared to the findings of the control and interventional coronary CT scan.
Study design:	Open-label, non-randomised
Inclusion / Exclusion criteria:	Inclusion - Patients referred for cardiac CT angiography - Age ≥ 18 years - Written informed consent Exclusion - Pregnancy or breast-feeding - Enrollment of the investigator, his/her family members, employees and other dependent persons - Renal insufficiency (GFR below 35 mL/min/1.73 m²)

Measurements and procedures:	The intervention is an additional cardiac CT angiography scan with 20-50% lower radiation exposure immediately after the clinical scan
Study Product / Intervention:	Deep-learning image reconstruction
Control Intervention (if applicable):	Clinically indicated cardiac CT angiography
Number of Participants with Rationale:	50 patients Considering the impact of gender, body habitus, BMI and heart rate a broad spectrum of patients should be scanned. Based on clinical experience and previous publication, 50 patients should provide valid results
Study Duration:	2 months
Study Schedule:	Start (first patient): May 1st 2019 End (last patient, last visit): June 9th 2019
Investigator(s):	See separate staff list
Study Centre(s):	Single-centre
Statistical Considerations:	The statistical analysis will include correlation analysis and Bland-Altman analysis. Outcomes will be compared using Wilcoxon signed ranktest or other suitable tests. A P-value <0.05 will be considered statistically significant.
GCP Statement:	This study will be conducted in compliance with the protocol, the current version of the Declaration of Helsinki, the ICH-GCP or ISO EN 14155 (as far as applicable) as well as all national legal and regulatory requirements.

ABBREVIATIONS

AE	Adverse Event
CA	Competent Authority (e.g. Swissmedic)
CEC	Competent Ethics Committee
ClinO	Clinical Trials Ordinance
CRF	Case Report Form
eCRF	Electronic Case Report Form
CCTA	Coronary Computer Tomography Angiography
CTCAE	Common terminology criteria for adverse event
DLIR	Deep-learning image reconstruction
H0	Null hypothesis
H1	Alternative hypothesis
IMD	Investigational Medical Device
ISF	Investigator Site File
ITT	Intention to Treat
LHR	Law on human research
PI	Principal Investigator
SAE	Serious Adverse Event
SDV	Source Data Verification
SNCTP	Swiss National Clinical Trial Portal
SOP	Standard Operating Procedure
TMF	Trial Master File

STUDY SCHEDULE

	1 **Day 1** (Scanning)
Participant Information and Informed Consent	√
Inclusion- and Exclusion Criteria	√
Demographic Data	√
Medical History / Concomitant Diseases	√
Serious Events	√
Non-contrast enhanced cardiac CT examination (clinically indicated)	√
Contrast enhanced cardiac CT examination (clinically indicated)	√
Lower-dose contrast enhanced cardiac CT examination (study scan)	√

1. STUDY ADMINISTRATIVE STRUCTURE

1.1 Sponsor, Sponsor-Investigator

PD Dr. med. Ronny Ralf Büchel

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Nuklearmedizin NUK A 12

Rämistrasse 100, 8091 Zürich

Email: ronny.buechel@usz.ch

Tel: 044 255 10 59

Fax: 044 255 44 14

Dr. med. R. Büchel will be involved in the screening process, obtaining informed consent, data analysis, statistics, quality control and furthermore he will be involved in the writing process.

1.2 Principal Investigator(s)

Same as sponsor

1.3 Statistician ("Biostatistician")

The statistical analysis will be performed by the members of our research group.

1.4 Monitoring Institution

Monitoring will be performed through the study coordination office according to our internal SOP's.

1.5 Data Safety Monitoring Committee

There is no need for a data safety monitoring committee because the patient are referred for a clinically indicated cardiac CT and the additional CT scans are performed identically to the clinical standard CT except with a lower radiation dose.

2. ETHICAL AND REGULATORY ASPECTS

Before this study will be conducted, the investigation plan, the proposed participant information and consent form as well as other study-specific documents will be submitted to a properly constituted Competent Ethics Committee (CEC) in agreement with local legal requirements, for formal approval. Any amendment to the investigation plan must as well be approved.

The decision of the CEC concerning the conduct of the study will be made in writing to the Sponsor-Investigator before commencement of this study. The clinical study can only begin once approval from all required authorities has been received. Any additional requirements imposed by the authorities shall be implemented.

2.1 Study registration

The study will be registered in the Swiss Federal Complementary Database („Portal") and in the international trial registry ClinicalTrials.gov (clinicaltrials.gov).

2.2 Categorisation of study

Category A:

- The deep-learning image reconstruction which is used in this study is CE marked and
- CT scans are performed according to the specialized information and clinical routine, but with lower tube current and/or tube voltage resulting in a lower radiation dose exposure. However, all scan parameters will lie within the specifications of the CE-marked CT Revolution scanning device.

2.3 Competent Ethics Committee (CEC)

Approval from the appropriate constituted Competent Ethics Committee is sought for each study site in the clinical trial. The reporting duties and allowed time frame are respected. No substantial changes are made to the investigation plan without prior Sponsor, CEC, CA approval, except where necessary to eliminate apparent immediate hazards to study participants.

Premature study end or interruption of the study is reported within 15 days. The regular end of the study is reported to the CEC within 90 days, the final study report shall be submitted within one year after study end. Amendments are reported according to chapter 2.10.

2.4 Competent Authorities (CA)

No approval from Swissmedic is necessary for this category A clinical trial.

2.5 Ethical Conduct of the Study

The study will be carried out in accordance with principles enunciated in the European Directive on medical devices 93/42/EEC and the ISO Norm 14155 and ISO 14971, the Swiss Law and Swiss regulatory authority's requirements. CEC will receive annual safety and interim reports and be informed about study stop/end in agreement with local requirements.

2.6 Declaration of interest

The department of nuclear medicine holds a research contract with GE Healthcare.

2.7 Patient Information and Informed Consent

The investigator must explain to each participant the nature of the study, its purpose, the procedures involved, the expected duration, the potential risks and benefits and any discomfort it may entail. Each participant must be informed that the participation in the study is voluntary and that he/she may withdraw from the study at any time and that withdrawal of consent will not affect his/her subsequent medical treatment.

The participant must be informed that his/her medical records may be examined by authorized individuals other than their treating physician.

All participants for this study will be provided a participant information sheet and a consent form describing this study and providing sufficient information for participants to make an informed decision

about their participation in this study.

The participant information sheet and the consent form will be submitted with the investigation plan for review and approval for the study by the CEC. The formal consent of a participant, using the approved consent form, must be obtained before that participant is submitted to any study procedure.

The participant should read and consider the statement before signing and dating the informed consent form, and should be given a copy of the signed document. The consent form must also be signed and dated by the investigator (or his designee) and it will be retained as part of the study records.

2.8 Participant privacy and confidentiality

The investigator affirms and upholds the principle of the participant's right to privacy and that they shall comply with applicable privacy laws. Especially, anonymity of the participants shall be guaranteed when presenting the data at scientific meetings or publishing them in scientific journals.

Individual subject medical information obtained as a result of this study is considered confidential and disclosure to third parties is prohibited. Subject confidentiality will be further ensured by utilizing subject identification code numbers to correspond to treatment data in the computer files.

Such medical information may be given to the participant's personal physician or to other appropriate medical personnel responsible for the participant's welfare, if the patient has given his/her written consent to do so.

For data verification purposes, authorized representatives of the Sponsor (-Investigator), a competent authority (e.g. Swissmedic), or an ethics committee may require direct access to parts of the medical records relevant to the study, including participants' medical history.

2.9 Early termination of the study

Provide a statement that the Sponsor-Investigator may terminate the study prematurely according to certain circumstances.

The Sponsor-Investigator may terminate the study prematurely according to certain circumstances, e.g.:

- when the safety of the participants is doubtful or at risk, respectively,
- alterations in accepted clinical practice that make the continuation of a clinical trial unwise,
- early evidence of benefit or harm of the experimental intervention

2.10 Protocol amendments

If an amendment to the investigational plan is to be made, it will be initiated by the PI and communicated to the investigators and all other involved persons through a short instructional meeting or if minor changes need to be implemented it could be done by e-mail.

Under emergency circumstances, deviations from the investigation plan to protect the rights, safety and well-being of human participants may proceed without prior approval of the sponsor and the CEC/CA. Such deviations shall be documented and reported to the sponsor and the CEC/CA as soon as possible.

All Non-substantial amendments are communicated to the CA as soon as possible if applicable and to the CEC within the Annual Safety Report (ASR).

3. BACKGROUND AND RATIONALE

3.1 Background and Rationale

Cardiac CT allows the assessment of the heart and of the coronary arteries by use of ionising radiation. Although radiation exposure was significantly reduced in recent years (1), further decrease in radiation exposure is limited by increased image noise and deterioration in image quality (2). Recent evidence suggests that further technological refinements with artificial intelligence allows improved post-processing of images with reduction of image noise (3).

The present study aims at assessing the potential of a deep-learning image reconstruction algorithm in a clinical setting. Specifically, after a standard clinical scan, patients are scanned with lower radiation exposure and reconstructed with the DLIR algorithm. This interventional scan is then compared to the standard clinical scan.

3.2 Investigational Product (treatment, device) and Indication

Medical Device (MD): TrueFidelity (Deep Learning Image Reconstruction, DLIR) software by GE Healthcare.

The medical device in question is a novel reconstruction algorithm for raw CT data which is based on artificial intelligence approaches, namely deep-learning iterative reconstruction (DLIR). This DLIR algorithm will be installed on the console of the CT Revolution scanning device, which is in routine clinical use for cardiac CT scans at the Department of Nuclear Medicine at the University Hospital Zurich. Purpose of this installation is the assessment of the performance of the DLIR algorithm during a limited time span of six weeks.

The algorithm will be CE-marked at the time of installation and use (statement by GE Healthcare provided separately). Its intended use is the reconstruction of CT datasets.

Of note, the novel DLIR algorithm will not substitute any clinical routine procedures currently in use. That is, diagnosis will still be made using the standard reconstruction algorithms.

3.3 Clinical Evidence to Date

Several studies have demonstrated the value of deep-learning in low-dose image reconstruction of CT scans (3). Several techniques of artificial intelligence were demonstrated to significantly reduce noise. Most promising are neural convolution networks. However, no study has yet been performed in a clinical setting of cardiac CT scanning.

3.4 Explanation for choice of comparator (or placebo)

The comparator is the clinically indicated, routinely performed CT using standard radiation dose.

3.5 Risks / Benefits

The cumulative additional radiation dose exposure arising from participation in this study is estimated to lie in the range of 0.4 mSv. In this range of radiation exposure, there is no known association with the risk of cancer. As the exposure is about 10% of background radiation exposure in Switzerland, it can be regarded as safe. Additionally, a second dose of iodinated contrast agent will be applied with the same volume used as for standard cardiac CT scanning. Depending on body habitus, the additional amount of contrast agent will lie in the range of 40-60 mL. Adverse reactions to iodinated contrast agents are allergic reactions and contrast-induced nephropathy. Regarding contrast reactions, there is no dose-dependent association. Hence, the risk for an allergic reaction is not expected to increase after the experimental scan. If patients show signs or symptoms of allergic reactions after the clinical scan, the experimental scan will not be performed. In contrast, a dose-dependent risk for contrast-induced nephropathy has been described in high-risk patients (4). However, in the present study, patients with reduced renal function (GFR below 35 mL/min/1.73 m^2) will be excluded. Furthermore, by applying a low-dose contrast protocol at our institution (5), the total volume of contrast agent applied after the clinical and experimental scan will be comparable to clinical routine in most institutions in Switzerland (i.e. 80-120 mL). Taken together, the additional exposure to the contrast agent can be considered as safe. Finally, the time needed to perform the additional CT scan is expected to be less than five minutes.

There is no immediate benefit for the participating patient. But the study results will allow us to implement in the future a scan protocol with a substantially lower radiation dose exposure which will ensure to the benefit of future patients referred for cardiac CT.

There are no anticipated adverse device effects according to EN ISO 14971 as the device itself is a post-processing tool. There are no possible interactions anticipated with concurrent medical interventions or with other competing trials.

3.6 Justification of choice of study population

All patients referred for a clinically indicated cardiac CT will in advance be informed by mail about the study. Written informed consent will be obtained on the day of examination prior to scanning.

For inclusion the patients must be ≥18 years of age. Pregnant or breast feeding females are excluded.

In the event of a participant incapable of judgment, or showing signs that he is unwilling to participate in the study will result in the patient being excluded from participation.

4. STUDY OBJECTIVES

4.1 Overall Objective

The overall objective is whether a deep-learning image reconstruction algorithm may improve image noise to the extent that radiation exposure can be lowered without impact on quantitative and qualitative image parameters.

4.2 Primary Objective

The primary objective is whether subjective image quality differs between the clinical and the interventional study CT scan.

4.3 Secondary Objectives

The secondary objective includes other measures related to image quality (e.g. image noise, image contrast) as well as further imaging parameters (e.g. radiation exposure, dose-length-product [DLP]) and assessment of coronary plaques and lesion severity differences between the clinical and the interventional CT scan.

4.4 Safety Objectives

As the additional CT scan is performed with less radiation dose but otherwise do not differ from the clinical routine, no safety concerns must be anticipated.

5. STUDY OUTCOMES

The present study assesses the impact of a deep-learning image reconstruction algorithm on image noise, image contrast, image quality and evaluation of coronary plaques and lesion severity.

5.1 Primary Outcome

Subjective image quality obtained from the experimental intervention with the control intervention.

5.2 Secondary Outcomes

Other measures related to image quality (e.g. image noise, image contrast)

Further imaging parameters (e.g. radiation exposure, DLP)

Impact on assessment of coronary plaques and lesion severity

5.3 Other Outcomes of Interest

Applicability and performance of established software (e.g. for quantitative plaque analysis, for calculation of endothelial shear stress or CTFFR) in images reconstructed with DLIR

The results of further diagnostic tests (e.g. invasive coronary angiography, myocardial perfusion imaging) that are triggered by the clinical coronary CT scan will be compared to the findings of the control and interventional coronary CT scan.

5.4 Safety Outcomes

None

6. STUDY DESIGN

6.1 General study design and justification of design

The above described study is an observational non randomized study, because the population eligible for this study is referred for a clinically indicated cardiac CT. All study patients will receive the same intervention and differences between standard and low dose protocol will be assessed for non-inferiority.**Methods of minimising bias**

The reconstructed images will have no annotations and therefore the clinicians evaluation the images will be blinded to scan settings.

6.2.1 Randomisation

Not applicable

6.2.2 Blinding procedures

The evaluation of the images will be blinded by switching the annotations of the images off.

6.3 Unblinding Procedures (Code break)

After analysis annotation will be recovered and screenshots are saved with annotations.

7. STUDY POPULATION

The study population consists of patients ≥18 years of age who are referred for cardiac CT.

7.1 Eligibility criteria

Subjects, who will fulfil all the following inclusion criteria, may be included into this project:

- Patients referred for coronary CT angiography
- Age >18 years
- Written informed consent

The presence of any one of the following exclusion criteria will lead to exclusion of the participant:

- Pregnancy or breast-feeding
- Enrolment of the investigator, his/her family members, employees and other dependent persons
- Renal insufficiency (GFR below 35 mL/min/1.73 m^2)

7.2 Recruitment and screening

Patients referred for a clinically indicated cardiac CT will receive prior to the date of their clinical exam the written patient information by mail. On the date of the clinical exam the patients will be consulted by a trained physician who will check again the eligibility criteria of the each patient and will explain again the purpose and the consequences of the study to the patient. If the patients still agree they will be asked to sign the informed consent form before scanning. The patients will not receive any financial compensation.

7.3 Assignment to study groups

Not applicable because there is only one single group.

7.4 Criteria for withdrawal / discontinuation of participants

Early withdrawal of the subject will occur upon patient request to not further participate in the study or if the CT images acquired during the study cannot be analyzed due to technical or other reasons. If discontinuation of a patient occurs he can be replaced by another subject.

8. STUDY INTERVENTION

8.1 Identity of Investigational Products (treatment / medical device)

The deep-learning image reconstruction by GE Healthcare is CE marked but not yet clinically available.

8.1.1 Experimental Intervention

The experimental intervention is an additional CT scan with a lower dose (about 20 to 50% decrease) and a similar contrast agent administration that is reconstructed with a deep-learning image reconstruction immediately after the clinical CT scan. The additional time required is about 5 minutes.

8.1.2 Control Intervention

The control intervention consists of the routinely performed cardiac CT datasets reconstructed with a standard iterative reconstruction algorithm (ASIR-V). Median radiation dose is about 0.5 mSv, range between about 0.2 and 1.2 mSv; median contrast agent administration about 45 mL, range between 35 and 55 mL.

8.2 Administration of experimental and control interventions

8.2.1 Experimental Intervention

The experimental intervention is an additional CT scan with a lower dose (about 20 to 50% decrease) and a similar contrast agent administration immediately after the clinical CT scan. The reconstruction by a deep-learning image reconstruction is performed after the scan at our department.

8.2.2 Control Intervention

The control intervention consists of the routinely performed cardiac CT datasets reconstructed with a standard iterative reconstruction algorithm (ASIR-V). Median radiation dose about 0.5 mSv, range between about 0.2 and 1.2 mSv; median contrast agent administration about 45 mL, range between 35 and 55 mL.

8.3 Dose / Device modifications

No modification to CE marked device application.

8.4 Data Collection and Follow-up for withdrawn participants

If a patient withdraws from the study after the acquisition of the images, the images will still be evaluated. In none of the participating patients a clinical follow-up will be performed which is in accordance with our clinical routine. The patients are clinically followed by their referring physicians.

8.5 Trial specific preventive measures

A urinary pregnancy test for women in childbearing age will be performed prior to study inclusion. Women with ovarectomy with or without hysterectomy and postmenopausal women (>12 months) are not considered as being in “childbearing age”.

8.6 Concomitant Interventions (treatments)

Not applicable

8.7 Study Drug / Medical Device Accountability

The medical device, namely the reconstruction software will be installed by engineers of the providing company GE Healthcare to ensure proper functionality and compliance with all regulatory aspects, including CE-marking of the device.

8.8 Return or Destruction of Study Drug / Medical Device

After the assessment phase of 6 weeks, the reconstruction software will be de-installed from our scanner systems until its official and commercial release.

9. STUDY ASSESSMENTS

9.1 Study flow chart(s) / table of study procedures and assessments

Time course:

1. Information of patient and written informed consent.
2. Evaluation of patient demographics, medical history (incl. risk factors, current symptoms, medication) and cardiac medical therapy are primarily based upon referral documents of the referring physician.
3. Body measurements (pulse, weight and height)
4. Urinary pregnancy test (for women in childbearing age*).
5. Check for inclusion and exclusion criteria.
6. Clinically indicated standard non-contrast CT image acquisition on the Revolution CT (GE Healthcare).
8. Clinically indicated cardiac CT scan according to clinical routine.
9. Followed by an additional study CT scan with a lower dose (about 20 to 50% decrease) and a similar contrast agent administration. This datasets will then be reconstructed with the DLIR algorithm.
10. Vital parameters (e.g., heart rate) and scanning parameters will be recorded.
11. After post-processing with the novel DLIR algorithm, parameters of image quality will be obtained from the reconstructed images along with exploratory analysis of additional image parameters. Additionally, applicability and performance of established softwares in images reconstructed with DLIR will be assessed, and the findings of the clinical and study CT will be compared to triggered other diagnostic tests.

* Women with ovarectomy with or without hysterectomy and postmenopausal women (>12 months) are not considered as being in "childbearing age".

The majority of the above mentioned measures are performed according to clinical routine. The only additional measures is the additional CT scan with lower dose and reconstruction with DLIR.

9.2 Assessments of outcomes

The Sponsor-Investigator is implementing and maintaining quality assurance and quality control systems with written SOPs and Working Instructions to ensure that research is conducted and data are generated, documented (record), and reported in compliance with the protocol, GCP, and applicable regulatory requirement(s).

All documents of the study will be stored for 10 years after the end of the study. Image data is stored and archived in the PACS system of the University Hospital Zurich according to clinical guidelines (10 years). Similarly, clinical data are stored in the patient information system (KISIM) o the University Hospital Zurich.

10. SAFETY

The Sponsor's SOPs provide more detail on safety reporting.

During the entire duration of the study, all serious adverse events (SAEs) are collected, fully investigated and documented in source documents. Study duration encompassed the time from when the participant signs the informed consent until the last investigation plan-specific procedure has been completed, and will end when the patient is leaving the nuclear department.

10.1 Medical Device Category A studies

Device deficiencies and all **adverse events (AE)** including all **serious adverse events (SAE)** are collected, fully investigated and documented in the source document and appropriate case report form (CRF) during the entire study period, i.e. from patient's informed consent until the last protocol-specific procedure, including a safety follow-up period. Documentation includes dates of event, treatment, resolution, assessment of seriousness and causal relationship to device and/or study procedure [ISO 14155, 6.4.1.].

Information on AEs is collected by clinical safety assessment at the study visit, as applicable and clinically justified in the context of the specific protocol. However, there are no foreseeable serious adverse events as a result of the DLIR.

Foreseeable serious adverse events due to the clinically indicated CT scan are allergic reactions to contrast agents or drop in blood pressure due to administration of betablocker and nitroglycerine after the clinically indicated scan. These rare events are treated as clinically indicated.

10.1.1 Definition and Assessment of safety related events

Adverse Event (AE)

Any untoward medical occurrence, unintended disease or injury or any untoward clinical signs (including an abnormal laboratory finding) in participants, users or other persons whether or not related to the investigational medical device [ISO 14155: 3.2].

Adverse Device Effect (ADE)

Adverse event related to the use of an investigational medical device [ISO 14155: 3.1].

Serious Adverse Event (SAE) [European regulation on medical devices 2017/745, art. 58].

Any adverse event that led to any of the following:

(a) death,
(b) serious deterioration in the health of the subject that resulted in any of the following:
  (i) life-threatening illness or injury,
  (ii) permanent impairment of a body structure or a body function,
  (iii) hospitalisation or prolongation of patient hospitalisation,
  (iv) medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function,
  (v) chronic disease,
(c) foetal distress, foetal death or a congenital physical or mental impairment or birth defect.

Device deficiency

Inadequacy of a medical device related to its identity, quality, durability, reliability, safety or performance, such as malfunction, misuse or use error and inadequate labelling [ISO 14155: 3.15].

Health hazards that require measures

Findings in the trial that may affect the safety of study participants and, which require preventive or corrective measures intended to protect the health and safety of study participants SAE [ClinO Art. 37].

Causal Relationship of SAE [MEDDEV 2.7/3 revision 3, May 2015].

A causal relationship towards the medical device or study procedure should be rated as follows:

- **Not related:** The relationship to the device or procedures can be excluded.
- **Unlikely:** The relationship with the use of the device seems not relevant and/or the event can be reasonably explained by another cause, but additional information may be obtained.
- **Possible:** The relationship with the use of the investigational device is weak but cannot be ruled out completely. Alternative causes are also possible.
- **Probable:** The relationship with the use of the investigational device seems relevant and/or the event cannot reasonably explained by another cause.
- **Causal relationship:** The serious event is associated with the investigational device or with procedures beyond reasonable doubt.

Device deficiencies that might have led to an SAE are always related to the medical device.

10.1.2 Reporting of Safety related events

Reporting to Sponsor-Investigator:

Health hazard that require measures are reported to the Sponsor-Investigator within 24 hours upon becoming aware of the event:

Pregnancies

Pregnancies are reported within a maximum of 24 hours to the Sponsor-Investigator. Pregnant patients are withdrawn.

Reporting to Authorities:

In Category A studies, the sponsor is subject to the notification requirements specified in Art. 15 of the MedDO of 17 October 2011 (SR 812.213).

It is the Investigator's responsibility to report to the Ethics Committee via BASEC **device deficiencies** that could have led to serious adverse events if suitable action had not been taken, intervention had not been made, or circumstances had been less fortunate within 7 days [ClinO Art. 42].

Health hazards that require measures are reported to the Ethics Committee via BASEC within 2 days [ClinO Art. 37].

Periodic safety reporting:

A yearly safety update-report is submitted by the Investigator to the Ethics Committee via BASEC.

A report is submitted to Swissmedic by the Sponsor-Investigator, as defined in Art. 15a,b of the MedDO of 17 October 2011 (SR 812.213).

11. STATISTICAL METHODS

11.1 Hypothesis

The hypothesis is that parameters of qualitative and quantitative image assessment do not differ between the clinical and the interventional scan.

11.2 Determination of Sample Size

Considering the impact of gender, body habitus, BMI and heart rate a broad spectrum of patients should be scanned. Based on clinical experience and previous publication, 50 patients should provide valid results (5).

11.3 Planned Analyses

The statistical analysis – performed in-house – will include correlation analysis and Bland-Altman analysis. Outcomes will be compared using Wilcoxon signed ranktest or other suitable tests. A P-value <0.05 will be considered statistically significant.

11.4 Handling of missing data and drop-outs

Incomplete datasets will be analyzed separately if occurring. Differences to main population might be analyzed using appropriate measure post-hoc, depending on amount of examination with missing data.

12. QUALITY ASSURANCE AND CONTROL

The Sponsor-Investigator is implementing and maintaining quality assurance and quality control systems with written SOPs and Working Instructions to ensure that trials are conducted and data are generated, documented (record), and reported in compliance with the protocol, EN ISO 14155, and applicable regulatory requirement(s).

Monitoring and Audits will be conducted during the course of the study for quality assurance purposes.

12.1 Data handling and record keeping / archiving

The study will strictly follow the investigation plan. If any changes become necessary, they must be laid down in an amendment to the investigation plan. All amendments of the investigation plan must be signed by the Sponsor-Investigator and submitted to CEC.

12.1.1 Case Report Forms

All patient data will be stored electronically in the form of an electronic Case Report Form (eCRF) within Redcap®. One form for each enrolled study participant, to be filled in with all relevant data pertaining to the participant during the study. All participants who either entered the study or were considered not-eligible or were eligible but not enrolled into the study additionally have to be documented on a screening log. The investigator will document the participation of each study participant on the Enrolment Log.

A declaration ensuring accuracy of data recorded in the case report forms must be signed by the investigator.

eCRFs must be kept current to reflect participant status at each phase during the course of study. Participants must not to be identified in the eCRF by name. Appropriate coded identification (e.g. Participant Number) must be used.

It must be assured that any authorized person, who may perform data entries and changes in the CRF, can be identified. A list with signatures and initials of all authorized persons will be filed in the study site file (included in the trial master file).

The investigators assure to perform a complete and accurate documentation of the participant data in the eCRF. Essential documents must be retained for at least 10 years after the regular end or a premature termination of the respective study (KlinV Art. 45).

Any patient files and source data must be archived for the longest possible period of time according to the feasibility of the investigational site, e.g. hospital, institution or private practice.

12.1.2 Specification of source documents

The following documents are considered source data, including but not limited to:

- SAE worksheets
- Medical records from other department(s), or other hospital(s), or discharge letters and correspondence with other departments/hospitals,
- Clinical information system (KISIM) entries (including ECG information)
- Image data from the scanners or analysis stations, stored in the intern PACS.

Source data must be available at the site to document the existence of the study participants and substantiate the integrity of study data collected. Source data must include the original documents relating to the study, as well as the medical treatment and medical history of the participant.

The following information (at least but not limited to) should be included in the source documents:

- Demographic data (age, sex)
- Inclusion and Exclusion Criteria details
- Participation in study and signed and dated Informed Consent Forms
- Visit date
- Medical history
- Results of relevant examinations
- Reason for premature discontinuation

Following data are considered for direct data entry into the CRF without separate source data:

- Current symptoms
- Medication and other medical therapies
- Risk factors
- Plaque characteristics and stenosis severity
- Image quality

12.1.3 Record keeping / archiving

All study data must be archived for a minimum of 10 years after study termination or premature termination of the clinical trial.

12.2 Monitoring

Regular quality control visits at the investigator's site prior to the start and during the course of the study will help to follow up the progress of the clinical study, to assure utmost accuracy of the data and to detect possible errors at an early time point. Because the current study is considered low risk, we will organize the quality control within our department. It will be conducted via study coordination office of our department which is not directly involved in this study.

All original data including all patient files, progress notes and copies of laboratory and medical test results must be available for quality control. Before study start a quality control plan will be set-up according to our standard procedures.

12.3 Audits and Inspections

A quality assurance audit/inspection of this study may be conducted by the competent authority or CEC, respectively. The quality assurance auditor/inspector will have access to all medical records, the investigator's study related files and correspondence, and the informed consent documentation that is relevant to this clinical study.

The investigator will allow the persons being responsible for the audit or the inspection to have access to the source data/documents and to answer any questions arising. All involved parties will keep the patient data strictly confidential.

12.4 Confidentiality, Data Protection

Direct access to source documents will be permitted for purposes of monitoring, audits and inspections. Only study team members and quality control team members have access to study related source data unless relevant for clinical routine.

12.5 Storage of biological material and related health data

Not applicable

13. PUBLICATION AND DISSEMINATION POLICY

After the statistical analysis of this trial the sponsor will make every endeavor to publish the data in a medical journal. Trial results will not be communicated to the individual participant.

14. FUNDING AND SUPPORT

14.1 Funding

The project will not be funded by external sources. It will be funded by the department of Nuclear Medicine.

14.2 Other Support

The Nuclear Medicine Department and UZH holds a general research contract with GE healthcare, but not direct monetary support for this study is given.

15. INSURANCE

Insurance is covered by "Versicherung für klinische Versuche und nichtklinische Versuche" by Zürich Versicherungs-Gesellschaft AG (Policy no.: 15.369.591).

Any damage developed in relation to study participation is covered by this insurance. So as not to forfeit their insurance cover, the participants themselves must strictly follow the instructions of the study personnel. Medical emergency treatment must be reported immediately to the investigator. The investigator must also be informed instantly, in the event of health problems or other damages during or after the course of study intervention.

The investigator will allow delegates of the insurance company to have access to the source data/documents as necessary to clarify a case of damage related to study participation. All involved parties will keep the patient data strictly confidential.

A copy of the insurance certificate will be placed in the Investigator's Site File.

16. REFERENCES

1. Benz DC, Gräni C, Hirt Moch B et al. Minimized Radiation and Contrast Agent Exposure for Coronary Computed Tomography Angiography: First Clinical Experience on a Latest Generation 256-slice Scanner. Acad Radiol 2016;23:1008-14.
2. Benz DC, Fuchs TA, Gräni C et al. Head-to-head comparison of adaptive statistical and model-based iterative reconstruction algorithms for submillisievert coronary CT angiography. Eur Heart J Cardiovasc Imaging 2017.
3. Sahiner B, Pezeshk A, Hadjiiski LM et al. Deep learning in medical imaging and radiation therapy. Med Phys 2019;46:e1-e36.
4. Toprak O. Conflicting and new risk factors for contrast induced nephropathy. J Urol 2007;178:2277-83.
5. Benz DC, Gräni C, Hirt Moch B et al. A low-dose and an ultra-low-dose contrast agent protocol for coronary CT angiography in a clinical setting: quantitative and qualitative comparison to a standard dose protocol. Br J Radiol 2017;90:20160933.