Clinical Study Protocol **GE Healthcare**
CLA-17-01
GE-248-001

Title: A study of pattern of use for gadolinium-based contrast agents (GBCAs) in patients undergoing contrast-enhanced magnetic resonance (CE-MR) examination - a cross-sectional, multicentre, observational study with prospective data collection

Sponsor

GE Healthcare Ltd. and its Affiliates (hereinafter referred to as the "sponsor")

EU PAS Registration Number: EUPAS21473

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Confidentiality Statement

Investigator's Signature Page

I have read this protocol and all associated case report forms and agree to conduct this study in full accordance with the stipulations of the protocol described herein.

Signature Investigator / Principal Investigator of the Centre	Date
Print Name	

1 SYNOPSIS

<table>
<tr><td>Name of Sponsor/Company:
GE Healthcare Ltd. and its Affiliates</td><td rowspan="3">Individual Study Table Referring to Part of Dossier in Which the Individual Study or Study Table is Presented:

Volume:

Reference:</td><td rowspan="3">(For National Authority Use Only)</td></tr>
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<tr><td colspan="3">Protocol Number: CLA-17-01</td></tr>
<tr><td colspan="3">Investigators and Study Centre(s): 14 centres in Europe: Germany (2 centres), Poland (3 centres), Spain (3 centres), Italy (3 centres), France (1 centre), Norway (1 centre), Portugal (1 centre).</td></tr>
<tr><td colspan="3">Phase of Development: Observational post-marketing study</td></tr>
<tr><td colspan="3">Objectives:
The GBCA observational study, will prospectively collect data on the pattern of use for GBCA in real-life diagnostic settings with special reference to Clariscan after its commercial launch in Europe.
Primary Objective:
To understand the pattern of use of GBCAs in magnetic resonance imaging (MRI) centres in Europe.
Secondary Objective:
To assess the effectiveness and safety profile of GBCAs, including Clariscan, in real-life settings.</td></tr>
<tr><td colspan="3">Study Design:
A cross-sectional, multicentre, observational study with prospective data collection in patients undergoing CE-MR examination as part of routine clinical practice. Patients will be invited to participate in the study only after the decision has been made by the physician to use contrast agents and Clariscan is already included in the formulary of the hospital/institution as an independent decision prior to investigator taking part in this study. Patients enrolled in the study will not be actively followed up to collect adverse events (AEs) or outcomes. Any spontaneously reported AEs/information will be recorded/reported by the investigators up to 7 days after the magnetic resonance (MR) procedure.</td></tr>
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Selection of Centres, Investigators, and Subjects:

Inclusion Criteria:

Centre Criteria

A centre will be eligible for this observational study if all of the following apply:

- Centre included Clariscan on the formulary for MR examinations.
- Have electronic record of cumulative data and are willing to report the cumulative data at the end of the recruitment period.

Investigator Criteria

An investigator will be eligible for this observational study if all of the following apply:

- The MR radiologist is competent to perform and report MR examinations.
- Nurse/radiology technician and other members of his/her team are willing to participate in the relevant assessments outlined in this protocol.
- No other radiology team has been selected to take part in this study from this centre.

Where a radiology team has multiple physicians involved in the patients' diagnosis and contrast media selections, the radiology team should appoint a single overarching Principal Investigator of the Centre**.** Alternatively, the study can be focused on a specific patient group under the responsibility of a single physician, as most appropriate to the local circumstances.

Patient Criteria

A patient will be eligible for this observational study if all of the following apply:

- Male/Female patients of all age groups.
- Patients of all pathologies who require CE-MR imaging as part of their diagnostic work up and the radiologist/physician has made the decision to use extracellular GBCAs as part of routine clinical practice.
- Provided informed consent (directly or via a legal representative) to participate in the study.

GBCA Exclusion Criteria:

- Use of liver-specific GBCAs (Primovist and MultiHance when used for liver excretion properties).*

Note for exclusion criteria:

Please note if GBCAs are used off label in clinical practice for patients in indications not listed in the Summary of Product Characteristics (SPC), these will be reported as off label use.

*For liver-specific GBCAs used (where excretion by the hepatocytes is the mechanism as opposed to extracellular) no patient or procedure level data will be collected and these patients will also not be included in the subgroup of patients where image transfer will be done. There is no plan to do image assessment for image performed by liver-specific contrast media as Clariscan does not have this indication and is not excreted by the liver. MultiHance, when used for liver excretion properties, will also not be included, but for all other indications it will be included for full data collection.

However, when reporting the overall number of MR procedures for the entire centre and for the investigator participating in the study, liver-specific agents will be reported in the cumulative data as the number of procedures done by liver-specific agents.

Number of Subjects/Centres Planned: Up to 5,400 patients in 14 centres in Europe: Germany (2 centres, 300-600 patients per centre), Poland (3 centres, 300 patients), Spain (3 centres, 200-500 patients), Italy (3

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centres, 100-500 patients), France (1 centre, 250 patients), Norway (1 centre, 200 patients), Portugal (1 centre, 300 patients).

CE-MR Imaging of Subjects:

- **Medicinal Product:** Clariscan as per SPC; other GBCAs as prescribed
- **Duration of Treatment:** at the time of injection of GBCA and immediately after that with spontaneous reporting of AEs up to 7 days; no active follow-up

Pattern of Use, Effectiveness, and Safety Variables

Pattern of GBCA Use:

The pattern of use for GBCAs including Clariscan for MR (MR angiography [MRA]/MRI) examination will be assessed based on the following variables:

1. The number of radiological procedures, including ultrasound, MR, computed tomography (CT) scan, fluoroscopy, X-ray, single-photon emission CT (SPECT), and positron emission tomography (PET) examinations, performed by the study centre during the recruitment period of the study. The number of procedures done by the study centre will be collected once in the study and will be used to assess the percentage and proportion of different procedures performed by the radiology department, including the percentage of MR procedures with or without GBCAs (total GBCAs and individual GBCA).
2. Number of MR machines and staff (nurses and technicians) will be recorded to assess the workload per MRI machine and staff.
3. The number of radiological procedures, including ultrasound, MR, CT scan, fluoroscopy, X-ray, SPECT, and PET examinations, reported by the investigator during the recruitment period of the study. The number of procedures done by the centre will be used to assess the percentage and proportion of different procedures performed by the investigator (radiologist), including the percentage of MR procedures with or without GBCAs (total GBCAs and individual GBCA).
4. Use of GBCAs – Total and individual GBCA (generic GBCA recorded as a separate entity) use as per indication, organ/system imaged, age, gender, body mass index (BMI; <18 is "underweight", 18 to 25 is "normal", 26 to 30 is "overweight", 30 to 40 is "obese", and >40 is "morbidly obese"), reason for use of GBCA and preference for a particular GBCA due to BMI.
5. Referral pattern for CE-MRI – the following information will be assessed:
    a. Referring physician
        1. seniority (house officer or equivalent, registrar, consultant, super specialist)
        2. specialty (e.g., cardiologist oncologist)
    b. The quality of referral will be assessed by the radiologist as follows:
        1 = not enough information
        2 = have all necessary information
        3 = good full detailed information with clear question
6. Repeat MR examinations done will be reported with the reason for repeat examination. Repeat examination will be defined as an MR examination for the same indication/reason as for the first examination, not follow-up MR or MR examination to answer a different question. In addition, assessment will be made for individual GBCA.
7. Assessment of the referral note recorded verbatim in the open text section will be assessed qualitatively

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for emerging themes and patterns.

8. Challenges for radiology department will be assessed qualitatively for emerging patterns and themes.

Effectiveness Assessments:

1. **Stage 1- Assessment by local radiologist/technician/nurse:** Three parameters will be assessed for effectiveness of GBCAs, including Clariscan, by local radiologist (a & b) and technician/nurse (c) as first stage of assessment:
    a) Image quality reported by the local radiologist.
    b) Diagnostic confidence reported by the local radiologist.
    c) Customer satisfaction survey reported by the local nurse/radiology technician recorded once per centre during the study for each GBCA used at the study centre, including generics.
2. **Stage 2 - Assessment by expert panel:** The second stage of analysis will be performed at a later date on a subgroup of patients. The anonymised images will be blindly analysed by an expert MR radiologist panel to assess the quality of images. The first 50 images will be analysed in a 1:1 ratio for Clariscan and other GBCAs, i.e., the first consecutive 25 images for Clariscan and the first consecutive 25 images of the other GBCAs (excluding liver-specific GBCAs). In total, a maximum of 850 patients' images will be transferred from all study centres. If sufficient number of images (25) for Clariscan or other GBCA group are not acquired in 3 months, the recruitment will stop at 3 months and all images for either group will be transferred for blinded read.
   Images will be assessed for: a) Quality of images reported by 3 MR expert radiologists blinded to the GBCAs use and inter-observer variability, and b) Correlation between local radiologist rating and blinded radiologist rating.

Safety assessment:

Safety assessment will be based on spontaneously reported AEs for all GBCAs, including Clariscan. AE collection for spontaneously reported AEs and serious AEs (SAEs) will begin at the time of contrast medium injected and continue up to 7 days after GBCA use for individual patient, unless consent is withdrawn. AEs reported in the first hour after administration will be reported as "immediate" and any AEs reported after 1 hour and up to 7 days will be recorded as "delayed". All AEs will be tabulated as number reported and percentage:

1 AEs, SAEs, severity of AEs, Clariscan vs GBCAs

2 AEs, SAEs, severity of AEs, Clariscan vs individual GBCA

Statistical Methods and Planned Analysis:

Pattern of Use Analyses:

The pattern of use for GBCAs for MR (MRA/MRI) examination will be summarised for all GBCAs pooled, for non-Clariscan GBCAs pooled, and for all individual GBCAs administered during the study, including Clariscan. The overall pattern of use will be assessed based on summary data from a number of different centre, investigator, and patient-level variables as outlined below.

A qualitative analysis of these variables will be performed describing the overall pattern of use, referral pattern, and challenges in a radiological practice.

Centre and Investigator Variables:

The following summaries will be provided, separately, for the Centre and the Investigator Analysis Sets:

- The average number of radiological procedures performed overall by [centres/investigators, respectively]

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during the recruitment period of the study.

- The average number of each type of radiological procedure (ultrasound, MR, CT scan, fluoroscopy, X-ray, SPECT, and PET examinations) performed by [centres/investigators, respectively] during the recruitment period of the study.
- The average percentage of each type of radiological procedure performed by [centres/investigators, respectively] during the recruitment period of the study as a proportion of the overall number of radiological procedures performed during the same period. The overall number of procedures from the centre will act as a denominator for the calculation of percentage and proportions of individual types of procedures.

The following additional information will be collected for the Centre Analysis Set:

- The average number of MR machines and staff (nurses and technicians) utilised by centres during the recruitment period of the study.

The following additional information will be collected for the Investigator Analysis Set:

- The average number of enhanced and non-enhanced procedures performed by investigators during the recruitment period of the study.

Patient-Level Variables:
The following summaries will be provided for the Full Analysis Set:

- The number of times a GBCA was used per indication, organ/system imaged, age, gender, BMI, reason for use of GBCA and preference for a particular GBCA.
- The number of each type of referring physician (seniority or specialty).
- The quality of the referral during the recruitment period of the study.
- The number of repeat MR examinations that are performed during the recruitment period of the study and a summary of the reasons for repeat exams.

Efficacy Variables and Analyses:
Effectiveness data will be summarised for all GBCAs pooled, for non-Clariscan GBCAs pooled, and for all individual GBCAs administered during the study, including Clariscan. Statistical differences in image quality and diagnostic confidence between groups (Clariscan vs non-Clariscan GBCAs pooled and Clariscan vs each individual GBCA) will be assessed at an alpha of 0.05. However, no formal statistical hypotheses will be tested and no adjustments will be made for multiplicity.

The following summaries will be provided for the Effectiveness Analysis Set:

- The average image quality.
- The average change in diagnostic confidence (diagnostic confidence using CE-MR enhanced image minus diagnostic confidence using the non-enhanced image).
- The proportion of patients for whom contrast-enhanced MRI changed the diagnosis (asked as a yes/no question on the eCRF).
- The proportion of patients for whom contrast-enhanced MRI increased the confidence in diagnosis (asked as a yes/no question on the eCRF).

Safety:

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AEs will be summarised for all GBCAs pooled, for non-Clariscan GBCAs pooled, and for all individual GBCAs administered during the study, including Clariscan. AEs and SAEs will be coded using Medical Dictionary for Regulatory Activities (MedDRA) and all reported events will be listed for the Safety Analysis Set. Immediate treatment-emergent AEs (TEAE) are defined as AEs that occur from the time of treatment administration through 1 hour after administration. Delayed TEAEs are defined as AEs that occur later than 1 hour post-administration up to 7 days post-administration.

The number and percentage of patients with 1 or more AEs will be summarised by system organ class and preferred term. Summaries will also be presented by AE intensity and judged relationship to study drug. Treatment-emergent SAEs will be presented by treatment group for the safety population.

Sample Size:

This is an observational study to understand the pattern of use of GBCAs use in CE-MR. The sample size is not based on statistical considerations, as the study does not formally test a hypothesis. Recruitment will be open for 3 months (90 days), with a cap on the maximum number of patients recruited by each centre (Table 1), and all consecutive patients who provide informed consent from the start of study (after Clariscan is on formulary in the study centre and available for routine clinical use) will be enrolled. Even if the centre has not enrolled the maximum number of patients allocated for that centre, recruitment will close at the end of the 90-day enrolment period regardless of the number of patients enrolled. It is anticipated that up to 5,400 patients from European countries where Clariscan has been launched will be enrolled. The maximum number of patients per country can be found in Table 1.

Table 1 Maximum Number of Patients Per Country

Country	Number of Centres	Maximum Number of Patients Allocated to Centres
Norway	1	200
Germany	2	300 + 600 = 900
Spain	3	500 x 2 + 200 = 1200
Italy	3	500 + 400 + 100 = 1000
Portugal	1	300
France	1	250
Poland	3	300 x 3 = 900

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3 LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

AE	Adverse event
BMI	Body mass index
CA	Competent Authorities
CE-MR	Contrast-enhanced magnetic resonance
CKD	Chronic kidney disease
CRO	Contract research organisation
CT	Computed tomography
DSS	Drug Safety Surveillance
ECG	Electrocardiogram
eCRF	Electronic case report form
eGFR	Estimated glomerular filtration rate
EMA	European Medicines Agency
EMR	Electronic medical record
EU	European Union
FDA	Food and Drug Administration
FLAIR	Fluid attenuation inversion recovery
GBCA	Gadolinium-based contrast agent
GCP	Good Clinical Practice
GEHC	GE Healthcare
GFR	Glomerular filtration rate
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
MedDRA	Medical Dictionary for Regulatory Activities
MR	Magnetic resonance
MRA	Magnetic resonance angiography
MRI	Magnetic resonance imaging
PACS	Picture archiving and communication system
PET	Positron emission tomography
SAE	Serious adverse event
SOPs	Standard operating procedures
SPC	Summary of Product Characteristics
SPECT	Single-photon emission computed tomography
TEAE	Treatment-emergent adverse event
UK	United Kingdom

4 BACKGROUND INFORMATION

Magnetic resonance (MR) examination is fast emerging imaging modality in medical diagnostic field, approximately one third to half of the MR examinations are enhanced by contrast agents [Lin and Brown 2007], [Ferris and Goergen 2017]. Gadolinium-based contrast agents (GBCAs) are the most commonly, if not the only, MR contrast agents used in clinical practice in different indications and age groups. These agents have been used in 300 million patients worldwide since 1988 and can be differentiated based on chelate chemistry, stability, viscosity, osmolality, and in effectiveness for specific applications [ACR 2016]. Over the course of time GBCAs have faced challenges and controversies in the form of nephrogenic systemic fibrosis and gadolinium in brain which has affected their clinical use. In this climate, it is essential to understand how clinicians use GBCAs in clinical practice including the referral pattern, why enhance, how to select a contract agents, what attributes are important for clinicians in the decision-making process and understanding the process and practice in the real world.

Literature search through PubMed with no time limit and using term ("gadolinium"[MeSH Terms] OR "gadolinium"[All Fields]) AND ("utilization"[Subheading] OR "utilization"[All Fields] OR "use"[All Fields]), 124 studies were listed. A second search was done to include the surveys and questionnaires, reported 741 results ("gadolinium"[MeSH Terms] OR "gadolinium"[All Fields]) AND ("surveys and questionnaires"[MeSH Terms] OR ("surveys"[All Fields] AND "questionnaires"[All Fields]) OR "surveys and questionnaires"[All Fields] OR "survey"[All Fields]). All studies, surveys and questionnaires were not relevant. A few had some relevance but they focused on specific disease entities/patient groups and retrospective in methodology rather than prospective trials with overall assessment of contrast-enhanced MR imaging (MRI) use in a radiology department.

Moreover, given the recently published EU Commission decision of 23.11.2017 to suspend the approval of several linear gadolinium-containing contrast agents due to gadolinium deposits in the brain, the knowledge of how gadolinium-containing contrast agents are currently being used in practice is limited.

Quotation from the 21.07.2017 decision of the EMA (EMA/457616/2017):

> *The intravenous linear agents gadoxetic acid and gadobenic acid can continue to be used for liver scans because they are taken up in the liver and meet an important diagnostic need. In addition, gadopentetic acid given intra-articularly (into the joint) can continue to be used for joint scans because the dose of gadolinium used for joint injections is very low.*
>
> *All other intravenous linear products (gadodiamide, gadopentetic acid and gadoversetamide) should be suspended in the EU.*
>
> *Another class of gadolinium agents known as macrocyclic agents (gadobutrol, gadoteric acid and gadoteridol) are more stable and have a lower propensity to release gadolinium than linear agents. These products can continue to be used in their current*

indications but in the lowest doses that enhance images sufficiently and only when unenhanced body scans are not suitable.

It is currently unknown and of high scientific interest with which dosages the radiologists use the gadolinium-containing contrast media still available on the market. Such information, which is very important for the referring physicians, can only be obtained by up-to-date observation and documentation in the daily routine.

It is also currently unknown and of further interest for the assessment of the applications, which criteria referrers consider for the administration of gadolinium-containing contrast agents after the publication of the EMA/457616/2017 requirements. In particular, it is unknown whether the presence of pre-existing renal insufficiency is taken into consideration, how often MR contrast agents are used in the same patient and whether this is dependent on indication and/or comorbidities. For example, this question is relevant to patients evaluated for multiple sclerosis and cancers, where it is unknown if notwithstanding the known brain retention of gadolinium, repeated contrast enhanced MR scans are considered necessary. Also, it is unknown if dose reductions, perhaps dependent on scanner magnetic field strength, are applied.

The study plan/protocol and the resulting documentation sheet of the requested study accurately collects data useful to clarify these points and will therefore provide more accurate insight into the potentially adapted clinical procedure.

The primary objective of the GBCA observational study, will be to prospectively collect data on the pattern of use for GBCA in real-life setting with special reference to Clariscan after its commercial launch in Europe. In addition, as a secondary objective, the study will look at the effectiveness and safety profile of GBCAs including Clariscan in clinical practice.

5 STUDY OBJECTIVES AND PURPOSE

The GBCA observational study, will prospectively collect data on the pattern of use for GBCA in real-life diagnostic settings with special reference to Clariscan after its commercial launch in Europe.

The primary and secondary objectives of the study are as follows:

5.1 Primary Objective:

To understand the pattern of use of GBCAs in MRI centres in Europe.

5.2 Secondary Objective:

To assess the effectiveness and safety profile of GBCAs, including Clariscan, in real-life settings.

6 STUDY DESIGN

6.1 Overall Study Design and Plan

A cross-sectional, multicentre (17 European Union [EU] centres), observational study with prospective data collection in patients undergoing contrast-enhanced MR (CE-MR) examination as part of routine clinical practice. Patients will be invited to participate in the study only after the decision has been made by the physician to use contrast agents and Clariscan is already included in the formulary of the hospital/institution as an independent decision prior to investigator taking part in this study. Patients enrolled in the study will not be actively followed up to collect adverse events (AEs) or outcomes. Any spontaneously reported AEs/information will be recorded/reported by the investigators up to 7 days after the MR procedure.

Enrolment

Patients: patients will only be approached to participate in the study after the physician has decided to use GBCA as part of routine clinical practice. Only patients who provide consent (directly or via a person with legal responsibility) will then be included in the study. To enable an understanding of the benefit of GBCAs use in a real world clinical setting the study plan to capture information in a maximum of 5,400 consecutive patients after the study centre has accepted to use Clariscan as an independent decision.

Recruitment will be based on **time (maximum 3 months – a month is equal to 30 calendar days) with a cap of a maximum number of cases per centre by country as defined in** Table 1**.** It will include all consecutive patients from the start of study after the Clariscan is on formulary of the study centre and available for routine clinical use. The decision to use GBCAs in the study centre/investigator will be made independent of the study after the centre has included Clariscan in the hospital/institution formulary.

The first 25 consecutive patients for which Clariscan is used and the first 25 consecutive patients for which any other GBCAs (all together 25 patients) is used, the images will be transferred for storage to allow a blinded image to read by an expert MR radiology panel to be performed in a future analysis. If the recruitment is less than 25 for either group, then the total images done for the group (Clariscan or GBCAs) during the recruitment period will be transferred. If a patient has repeat imaging for technical reasons and the image is not readable and has been repeated for same indication/reason, then the second readable image will be transferred for storage and analysis.

Investigator: the MR Radiologist; one investigator per centre.
Where a radiology team has multiple physicians involved in the patients' diagnosis and contrast media selections, the site investigators should appoint a single overarching Principal Investigator of the Centre.
Alternatively the study can be focused on a specific patient group under the responsibility of a single physician, as most appropriate to the local circumstances. Cumulative information

collected for the investigator at the end of the study refers to his/her practice during the recruitment period of the study (date of first patient and date of last patient recruitment).

Centre: the institution, hospital or private centre where the study investigator is practicing during the study and patients are recruited for the study from the centre. Cumulative data will be recorded on the eCRF for this centre for the period of recruitment (date of first patient and date of last patient recruitment).

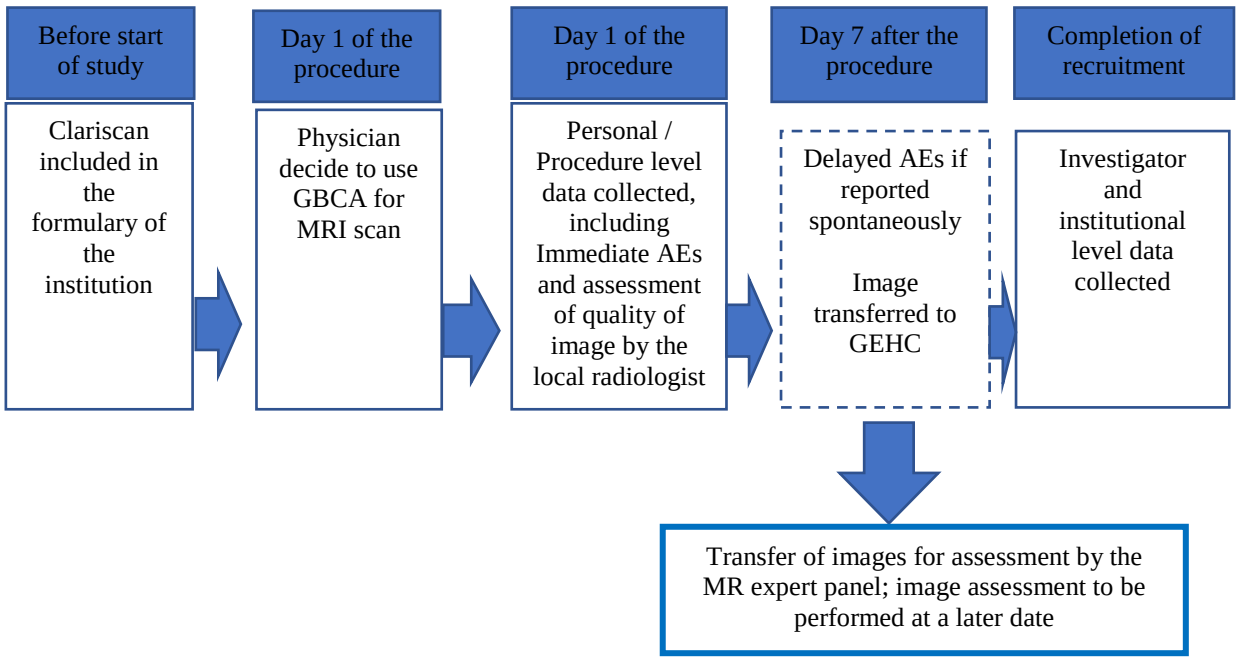
Centres with electronic medical record (EMR), picture archiving and communication system (PACS), or any other system in place to collect the cumulative data at the end of the study and compatible for image transfer.

Table 1 Maximum Number of Patients Per Country

Country	Number of Centres	Maximum Number of Patients Allocated to Centres
Norway	1	200
Germany	2	300 + 600 = 900
Spain	3	500 x 2 + 200 = 1200
Italy	3	500 + 400 + 100 = 1000
Portugal	1	300
Poland	1	300 x 3 = 900
France	1	250

An overview of study procedures is presented in Figure 1.

Figure 1 Study Diagram



6.2 Study Rationale

GBCAs are essential to enhanced the images in MR examinations. Over the course of time GBCAs have faced challenges and controversies. It is essential to understand how clinicians use GBCAs in clinical practice including the referral pattern, why enhance, how to select a contract agents, what attributes are important for clinicians in the decision-making process and understanding the process and practice in the real world.

The primary objective of the GBCA observational study, will be to prospectively collect data on the pattern of use for GBCA in real-life setting with special reference to Clariscan after its commercial launch in Europe. The data will be collected for CE-MR procedure and patients in detail to understand the clinical practice. To completely understand the overall picture of radiology practice in an institution the collective data of all radiological procedures by the investigator and the institution will be collected for the recruitment period. This will help understand what proportion of CE-MR procedures are performed by the investigator and institution.

A qualitative analysis will be performed describing the referral pattern and challenges in a radiological practice.

In addition, as a secondary objective, the study will look at the effectiveness reported as quality of images, diagnostic confidence and customer satisfaction reported on a Likert scale by the local radiologist/technician and spontaneously reported immediate and delayed AEs to assess the effectiveness and safety profile of GBCAs in clinical practice respectively.

During the study, the images will be collected and archived for the initial 50 cases from each investigation centre to be analysed separately at a later stage by a panel of 3 expert MR radiologists. The images will be assessed for the quality of images on the same scale as assessed by the local radiologist. The aim of this second, separate statistical analysis will be to assess the quality of images and see the inter-observer agreement by the expert MR radiologist and assess the agreement in quality of images between real-world reporting by the local radiologist and MR experts' assessment. This analysis will not be part of initial read out of the study due to lack of funding and will be performed at a later date. The current study will be an opportunity to collect and archive the images.

This study's safety monitoring plan is justifiable and adequate from a safety standpoint in view of the following:

- The design of the safety plan permits collection and comparison of the safety response to GBCAs in real life setting based on AEs reported voluntarily by the patient to the physician.

- Consideration of a 7-day documentation of AEs permits the evaluation of late-appearing adverse effects that may emerge or progress after the administration of GBCAs. In line with post-marketing requirements, the investigator will notify sponsor or regulatory authority of AEs he or she becomes aware of after the 7-day documentation interval.

- The measures used to assess effectiveness and safety are well-defined and reliable, and the proposed safety analyses are adequate to assess the effects of the administration of GBCAs.

6.3 Study Timeframe

The study will be initiated in January, 2018. Enrolment is expected to be completed by April 30, 2018.

Stage 2 analysis will not be part of the initial study read out, and will be performed at a later date.

6.4 Risks and Benefits to Subjects

GBCA observational study will only collect data for use of GBCAs including Clariscan as per clinical practice. No new procedure or intervention is recommended by the study protocol. There is no additional risk to the patients for taking part in the study. However, there is no direct benefit for the patient to take part in the study, but the understanding of the pattern of use, effectiveness and safety profile of GBCAs will improve the knowledge and understand of the MR procedures and will be beneficial for the society.

7 SELECTION AND WITHDRAWAL OF SUBJECTS

7.1 Procedures for Enrolment

After the start of the study all consecutive consenting adult and paediatric, male and female patients, undergoing MR procedures whose physician has made the decision to use GBCA as part of routine clinical practice will be enrolled. The enrolment of the total number of patients per centre will be limited to a defined number of patients for a centre (Table 1) with a maximum duration of recruitment of 3 months (month = 30days) from start date, i.e., first patient recruitment.

A subgroup of initial patients will be selected to transfer the anonymised images to GE Healthcare (GEHC) through AGMednet. The images will be archived at GEHC and analysed at a later date by an expert MR radiologist panel to assess the quality of images. The first 50 images will be transferred in a 1:1 ratio for Clariscan and other GBCAs, i.e., first consecutive 25 images (25 maximum or total recruited in 3 months) for Clariscan and other GBCAs. If sufficient number of images (25) for either group (Clariscan or other GBCAs) are not acquired in 3 months, the recruitment will stop at 3 months and all images will be transferred for the blinded read, the comparative analysis is not at centre level. All images will be pooled together for blinded image read by the expert panel.

7.2 Inclusion Criteria

7.2.1 Centre Criteria

A centre will be eligible for this observational study if all of the following apply:

- Centre included Clariscan on the formulary for MR examinations.
- Have electronic record of cumulative data and are willing to report the cumulative data at the end of the recruitment period.

7.2.2 Investigator Criteria

An investigator will be eligible for this observational study if all of the following apply:

- The MR radiologist is competent to perform and report MR examinations.
- Nurse/radiology technician and other members of his/her team are willing to participate in the relevant assessments outlined in this protocol.
- No other radiology team has been selected to take part in this study from this centre.

Where a radiology team has multiple physicians involved in the patients' diagnosis and contrast media selections, the radiology team should appoint a single overarching Principal Investigator of the Centre.
Alternatively the study can be focused on a specific patient group under the responsibility of a single physician, as most appropriate to the local circumstances.

7.2.3 Patient Criteria

A patient will be eligible for this observational study if all of the following apply:

- Male/Female patients of all age groups.
- Patients of all pathologies who require CE-MR imaging as part of their diagnostic work up and the radiologist/physician has made the decision to use extracellular GBCAs as part of routine clinical practice.
- Provided informed consent (directly or via a legal representative) to participate in the study

7.3 Exclusion Criteria

- Use of liver-specific GBCAs (Primovist and MultiHance when used for liver excretion properties).*

Note for exclusion criteria:

Please note if GBCAs are used off label in clinical practice for patients in indications not listed in the Summary of Product Characteristics (SPC), these will be reported as off label use.

*For liver-specific GBCAs used (where excretion by the hepatocytes is the mechanism as opposed to extracellular) no patient or procedure level data will be collected and these patients will also not be included in the subgroup of patients where image transfer will be done. There is no plan to do image assessment performed by liver-specific contrast medium as Clariscan does not have this indication and is not excreted by the liver. MultiHance, when used for liver excretion properties, will also not be included, but for all other indications it will be included for full data collection.

However, when reporting the overall number of MR procedures for the study centre and operating investigator, liver-specific agents will be reported in the cumulative data as the number of procedures done by liver-specific agents.

7.4 Withdrawal and Termination Criteria

7.4.1 Subject Withdrawal

There are no formal withdrawal criteria for this study. During the conduct of the study, the sponsor will review the safety data for trends and signals that would indicate the need for withdrawal of a subject.

In accordance with the Declaration of Helsinki, each subject is free to withdraw from the study at any time. Investigator(s) also have the right to withdraw subjects from the study in the event of illness, AEs, or other reasons concerning the health or well-being of the subject, or in the case of lack of co-operation.

Should a subject decide to withdraw after administration of the GBCA(s), or should the investigator(s) decide to withdraw the subject, all efforts will be made to complete and report the observations up to the time of withdrawal as thoroughly as possible. A complete final evaluation at the time of the subject's withdrawal should be made and an explanation given of why the subject is withdrawing or being withdrawn from the study.

The reason for withdrawal must be noted in the electronic Case Report Form (eCRF). If the reason for withdrawal is a clinical AE, monitoring will continue until the outcome is evident. The specific event or test result(s) must be recorded in the eCRF.

Subjects that withdraw will not be replaced.

7.4.2 Study or Site Termination

There are no formal termination criteria for this study. The sponsor reserves the right to terminate the study at any time.

8 IMAGING OF SUBJECTS

8.1 GBCAs Medicinal Product(s)

8.1.1 Clariscan 0.5 mmol/ml Solution for Injection

Clariscan 0.5 mmol/ml solution for injection will be administered as part of clinical practice according to the judgment of the site with regard to medical need. For more information, consult the SPC.

8.1.2 All GBCAs

Subjects will be administered a GBCA as part of clinical practice. All GBCAs will be selected by the sites and recorded as by the brand names.

8.1.3 Study Drug Accountability

No medicine will be provided by the Sponsor for the study. GBCAs will be used as part of clinical practice.

8.2 Method of Numbering Subjects and Assigning Subjects to Treatment Groups

Subject numbers will consist of 7 digits in total; the first 3 digits to identify the centre and the remaining 4 digits to identify the subject. Centre numbers will be in the format 001, 002, etc. Subject numbers for those who withdraw will not be reused.

Subjects will not be assigned to treatment groups because the choice of GBCA will be made by the investigator at the site as part of clinical practice.

8.3 Selection of Doses and Timing

Administration of Clariscan and MRI will be scheduled outside of this study as part of clinical practice; dosing and timing of imaging will have been selected at the discretion of the personnel at the imaging centre, also as part of clinical practice.

8.4 Blinding

This study is observational and no measures will be taken to try to blind participants.

8.5 Prior and Concurrent Therapy

Any medications taken by the subject within 24 hours of the MR examination through the end of the observation period will be recorded in the eCRF along with the indication. Either the generic or the trade name may be recorded.

8.6 Treatment Compliance

Not applicable to this study; all patients will be referred for a MR examination as part of clinical practice.

9 STUDY PROCEDURES

The MR examination will be performed as per routine clinical practice. The effectiveness and safety measurements obtained during the course of the study are summarised in the Study Schedule of Events (Table 2).

Table 2 Schedule of Assessments

Assessments	Enrolment Visit and Imaging Day 1	Day 7	Completion of Recruitment
Informed consent[1]	X		
Verify inclusion/exclusion criteria	X		
Enrolment and allocation of patient number	X		
Patient demographics, medical history, medication, and procedure information	X		
GBCA administration	X		
CE-MRI examination	X		
AEs/SAEs[2]	X	X	
Quality of image assessment by local radiologist-Likert scale	X		
Diagnostic confidence by local radiologist[3]	X		
Transfer of images	X	X	
Customer satisfaction by radiology technician/nurse			X
Investigator information - cumulative numbers for the recruitment period (date of the first patient to date of last patient at the centre) of the study at the centre			X
Centre information- cumulative numbers for the recruitment period (date of the first patient to date of last patient at the centre) of the study at the centre			X

AE = adverse event; SAE = serious adverse event

[1] Informed consent must be obtained before enrolment into the study.

[2] Adverse events (AEs) that occur in the first hour post-administration will be defined as “immediate”, and any AEs that occur >1 hour to 7 days post-administration will be defined as “delayed”.

[3] Diagnostic confidence to be recorded by the local radiologist before the CE MR scan and again after the CE MR scan results are read.

9.1 Enrolment Visit and Imaging (Day 1)

All subjects must both satisfy the inclusion criterion and not satisfy the exclusion criterion listed in Sections 7.2 and 7.3. The following information will be collected from each subject prior to administration of GBCA:

- Informed consent
- Inclusion/exclusion criteria

- Demographic data
- Relevant medical history (a condition that is either active at enrolment or adversely impacts the subject's condition at enrolment; i.e., renal and hepatic status, history of allergy, rash urticaria, neurological problems, asthma, bronchoconstriction)
- Any medications taken by the subject within 24 hours of the MR examination through the end of the observation period will be recorded in the eCRF along with the indication
- Adverse events

Waivers or protocol exceptions will not be granted prospectively by the sponsor under any circumstances. Any exceptions to protocol specified requirements will be considered as protocol deviations.

After the subject is enrolled, the CE-MR procedure will be performed as routine clinical practice and findings reported in the eCRF. Information about the dynamic images or delayed enhancement images will be added:

- Quality of image assessment to be recorded by local radiology using a Likert scale
- Diagnostic confidence to be recorded by the local radiologist. Diagnostic confidence will be assessed first using only the non-enhanced image and then again using the contrast-enhanced image.
- AEs (immediate and delayed)

9.2 Post-Imaging Period

Safety measurements will be performed from GBCA administration until 7 days post-administration for AEs reported voluntarily by the patient. No follow-up safety assessment is required unless AEs are reported spontaneously by the patient or healthcare providers. However, AEs will be documented in line with the requirements applicable for use of medicines in general, irrespective of the documentation window.

The following information will be collected once at the end of the study:

- Customer satisfaction to be recorded by the local nurse/radiology technician once per centre for each GBCA used at the study centre, including generics
- Investigator information - cumulative numbers for the recruitment period (date of the first patient to date of last patient at the centre) of the study at the centre
- Centre information- cumulative numbers for the recruitment period (date of the first patient to date of last patient at the centre) of the study at the centre

The first 25 consecutive patients where Clariscan is used and the first 25 consecutive patients where any other GBCAs (all together 25 patients) is used, the images will be transferred for storage to allow a blinded image read by the expert MR radiology panel to be performed in a future analysis. If the recruitment is less than 25 for either group, then the total images done for the group (Clariscan or GBCAs) during the recruitment period will be transferred. If a patient has repeat imaging for technical reasons and the image is not readable and has been repeated for same indication/reason, then the second readable image will be transferred for storage and future analysis.

See Section 10.3 and the Study Schedule of Events Table (Table 2) for further details.

10 PATTERN OF USE, EFFECTIVENESS, SAFETY, AND OTHER VARIABLES

10.1 Pattern of GBCA Use

The pattern of use for GBCAs including Clariscan for MR (MR angiography [MRA]/MRI) examination will be assessed based on the following variables:

1. The number of radiological procedures, including ultrasound, MR, computed tomography (CT) scan, fluoroscopy, X-ray, single-photon emission CT (SPECT), and positron emission tomography (PET) examinations, performed by the study centre during the recruitment period of the study. The number of procedures done by the study centre will be collected once in the study and will be used to assess the percentage and proportion of different procedures performed by the radiology department, including the percentage of MR procedures with or without GBCAs (total GBCAs and individual GBCA).

2. Number of MR machines and staff (nurses and technicians) will be recorded to assess the workload per MRI machine and staff.

3. The number of radiological procedures, including ultrasound, MR, CT scan, fluoroscopy, X-ray, SPECT, and PET examinations, reported by the investigator during the recruitment period of the study. The number of procedures done by the centre will be used to assess the percentage and proportion of different procedures performed by the investigator (radiologist), including the percentage of MR procedures with or without GBCAs (total GBCAs and individual GBCA).

4. Use of GBCAs – Total and individual GBCA (generic GBCA recorded as a separate entity) use as per indication, organ/system imaged, age, gender, body mass index (BMI; <18 is "underweight", 18 to 25 is "normal", 26 to 30 is "overweight", 30 to 40 is "obese", and >40 is "morbidly obese"), reason for use of GBCA and preference for a particular GBCA due to BMI.

5. Referral pattern for CE-MRI - Following information will be assessed:

    a. Referring physician

        1. seniority (house officer or equivalent, registrar, consultant, super specialist)

        2. specialty (e.g., cardiologist oncologist)

    b. The quality of referral will be assessed by the radiologist as follows:

        1 = not enough information

        2 = have all necessary information

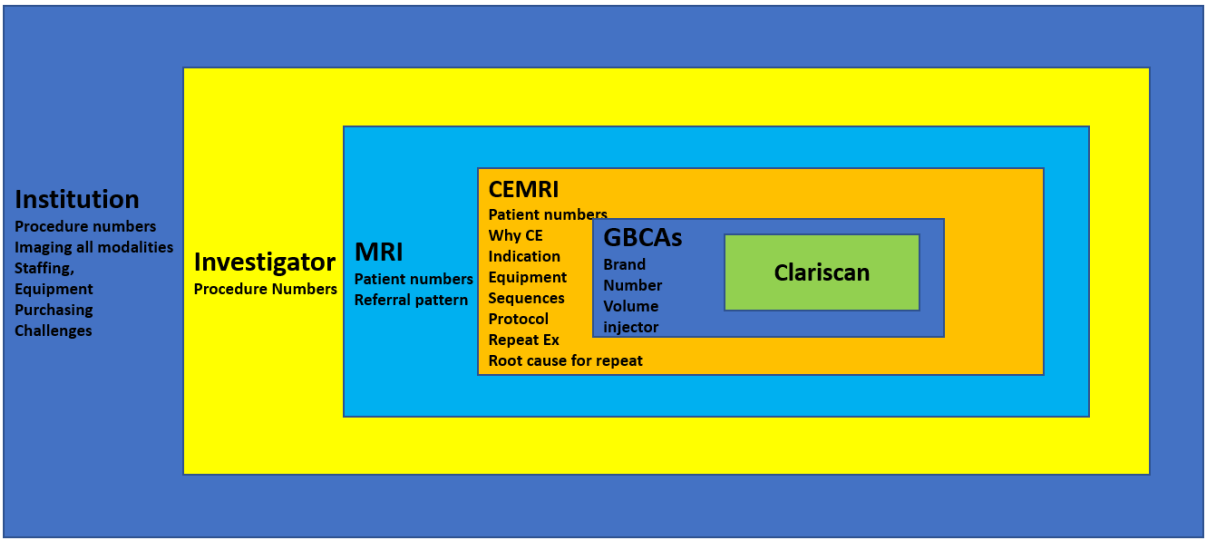
3 = good full detailed information with clear question

6. Repeat MR examinations done will be reported with the reason for repeat examination. Repeat examination will be defined as an MR examination for the same indication/reason as for the first examination, not follow-up MR or MR examination to answer a different question. In addition, assessment will be made for individual GBCA.

7. Assessment of the referral note recorded verbatim in the open text section will be assessed qualitatively for emerging themes and patterns.

8. Challenges for radiology department will be assessed qualitatively for emerging patterns and themes.

Figure 2 Pattern of Use



10.2 Effectiveness Assessments

Effectiveness will be assessed as Clariscan vs all GBCAs together and Clariscan vs individual GBCA. The assessment will be done in 2 stages:

Stage 1: by the local radiologist and nurse/technician

Stage 2: by a panel of 3 MR experts, blinded to the use of GBCAs independently for the first 50 images transferred to GEHC. The first 25 images of Clariscan and first 25 images all other GBCAs will be used for the analysis as 1:1 ratio. This analysis will be performed at a later date and not part of the initial read out of the study.

Stage 1

Three parameters will be assessed for effectiveness of GBCAs, including Clariscan, by local radiology (A & B) and technician/nurse (C) as first stage of assessment:

A- Image quality reported by the local radiologist.

B- Diagnostic confidence reported by the local radiologist.

C- Customer satisfaction survey reported by the local nurse/radiology technician recorded once per centre during the study for each GBCA used at the study centre, including generics.

A- Image quality reported by the local radiologist

Quality of image will be assessed by the local reporting radiologist on a 4-point Likert scale.

This is based on literature review for the assessment of CE-MR images. The definition for cardiovascular MRA and MRI images are on a 4-point Likert scale and defined in following section.

MRA: [Hansmann et al. 2014]: For the qualitative assessment, blinded readers assessed image quality on a scale of 1 to 4:

1 = poor image quality and blurring of the arterial segment

2 = fair image quality, inadequate arterial enhancement for confident diagnosis

3 = good image quality and arterial enhancement, adequate for confident diagnosis

4 = excellent image quality and arterial enhancement, for highly confident diagnosis

MRI: [Maravilla et al. 2017] used the following definition for overall visualisation and characterisation of the lesion (or most representative lesion, i.e., enhancing and/or largest if there was >1 lesion present) were assessed on a 4-point scale:

0 = poor, inadequate

1 = fair, partial

2 = good, adequate

3 = excellent

Based on the literature review in this study, image quality will be captured on the following 4-point scale:

	MRI	MRA
1	poor, inadequate;	poor image quality and blurring of the arterial segment;
2	fair, partial	fair image quality, inadequate arterial enhancement for confident diagnosis
3	good, adequate;	good image quality and arterial enhancement, adequate for confident diagnosis;
4	excellent	excellent image quality and arterial enhancement, for highly confident diagnosis)

The results will be reported as comparison of Clariscan to all GBCAs and Clariscan vs individual GBCA if the cohort is bigger than 100 cases.

B- Diagnostic confidence reported by the local radiologist

For each patient based on the **most representative lesion**. All available sequences (e.g., fluid attenuation inversion recovery [FLAIR], T2, and T1 with and without contrast administration) will be available for readers to review and evaluate. **Before reviewing the CE-MR image**, the radiologist will be asked to enter the confidence to make a diagnosis for the patient as a whole number between 0% to 100% based only on the non-enhanced image. The radiologist will then enter the diagnostic confidence as a whole number between 0% to 100% after the CE-MR scan results are read. This will be used to calculate the change in diagnostic confidence in this study by the local radiologist for all GBCAs including Clariscan. The results will be reported as comparison of Clariscan to all GBCAs and Clariscan vs individual GBCA if the cohort is bigger than 100 cases.

C- Customer satisfaction survey reported by the local nurse/radiology technician recorded once per centre during the study for each GBCA used at the study centre, including generics

Reported once per centre by MR nurse/technician from the investigator's staff - Quality of packaging including bottles, syringe, marking, pack size available. This will be recorded once for each GBCA used at the study centre as an overall impression and rated as:

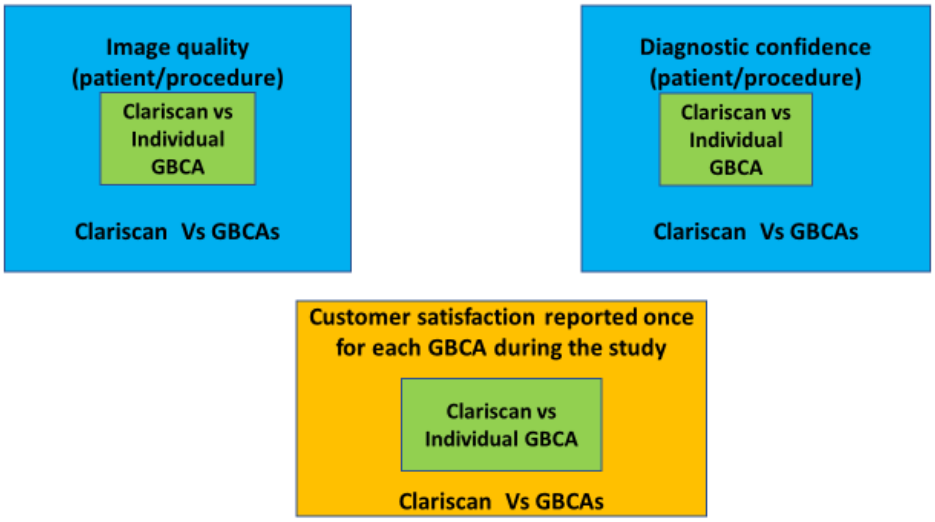
1 = can be improved

2 = good

3 = excellent

The results will be reported as comparison of Clariscan to all GBCAs and Clariscan vs individual GBCA.

Figure 3 Effectiveness Assessments



Stage 2 (to be performed at a later date): assessment by a panel of 3 MR experts, blinded to the use of GBCAs independently for the first 50 images transferred to GEHC. The first consecutive 25 images of Clariscan and first consecutive 25 images all other GBCAs will be used for the analysis as 1:1 ratio.

A subgroup of patients will be selected to transfer the anonymised images to GEHC through AGMednet. The images will be archived at GEHC to be analysed at a later date by an expert MR radiologist panel to assess the quality of images. The first 50 images will be transferred in 1:1 ratio for Clariscan and other GBCAs, i.e., the first consecutive 25 images for Clariscan and the first consecutive 25 images of the other GBCAs (excluding liver-specific GBCAs). In total, a maximum of 850 patients' images will be transferred from all study centres. If sufficient number of images (25) for Clariscan or other GBCA group are not acquired in 3 months, the recruitment will stop at 3 months and all images for either group will be transferred for blinded read.

- Collective anonymised and blinded images for all GBCAs including Clariscan from all centres will be assessed and analysed by a panel of 3 MR expert radiologists. There will be no centre-level analysis or comparison for Clariscan and other GBCAs.

- Quality of images reported by 3 MR expert radiologists blinded to the GBCAs use and inter-observer variability.

- Correlation between local radiologist rating and blinded radiologist rating.

This analysis will not be part of the initial read out of the study and will be performed at a later date.

10.3 Safety Assessments

Clariscan and any other GBCA used in this observational study are approved. Safety data will be collected, assessed and reported in accordance with post-marketing requirements. Clinical trial safety requirements do not apply.

The investigator(s) and the sponsor will review the safety data. The following safety data will be collected and evaluated:

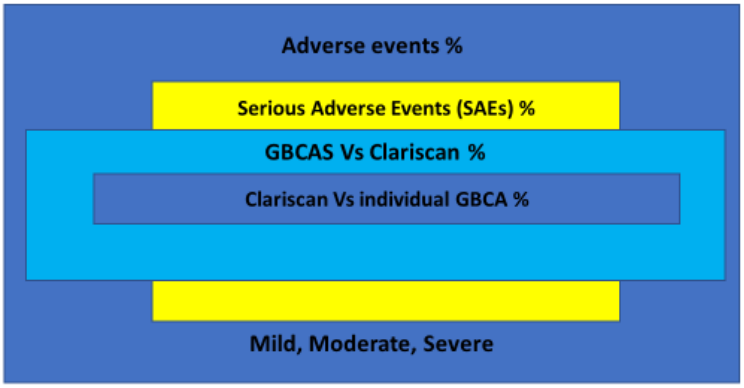
AE collection for spontaneously reported AEs and serious AEs (SAEs) will begin at the time of contrast medium injected and continue up to 7 days after GBCA use for individual patient, unless consent is withdrawn. AEs reported in the first hour post-administration will be recorded as "immediate" and any AEs reported after 1 hour and up to 7 days will be recorded as "delayed". Definition and examples of mild moderate and severe are mentioned in Section 15.2.

All AEs will be tabulated as number reported and percentage:

1 AEs, SAEs, severity of AEs, Clariscan vs GBCAs

2 AEs, SAEs, severity of AEs, Clariscan vs individual GBCA

Figure 4 Safety Profile



The radiological definition of 'immediate' and 'delayed' AEs and severity of AEs are in Section 15.2.

AE Definition: An AE is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a study drug, whether or not considered related to that product. Only symptoms/signs that begin or worsen in severity and/or frequency after GBCA administration/use will be recorded as AEs in the eCRF.

The subjects will be closely observed and questioned with non-leading questioning (e.g., "How do you feel?"). The subjects will be instructed to immediately report any symptoms and signs to the study staff (i.e., between formal observations).

Both the investigator(s) and sponsor/CRO will perform a causality assessment on any AE, to assess whether or not there is a reasonable possibility (evidence to suggest) that the GBCAs caused the event.

Adverse Reaction: An AE that is caused by the GBCA.

Suspected Adverse Reaction: A reasonable possibility exists for causality between the GBCA and the AE.

10.3.1 Serious Adverse Events

An SAE is defined as any AE that:

- Results in death.
- Is life-threatening.
- Requires in-patient hospitalisation or prolongation of existing hospitalisation.
- Results in persistent or significant disability or incapacity.
- Is a congenital anomaly or birth defect.
- Is another important medical event.*

(*Other important medical events are those that may not result in death, be life threatening, or require hospitalisation, but may be considered an SAE when, based upon appropriate medical judgment, they may jeopardise the subject and may require medical intervention to prevent one of the outcomes listed above. Other Significant AEs are clinical laboratory abnormalities that qualify as AEs (other than those meeting the definition for serious) and any events that lead to an intervention (including premature discontinuation of GBCA, dose reduction or significant additional concomitant therapy), other than those reported as SAEs, will be reported and evaluated as other significant AEs.

10.3.2 Adverse Event and Serious Adverse Event Reporting

Study centres are instructed to report all AEs to GEHC Global Pharmacovigilance within 3 days by sending an email to gpv.drugsafety@ge.com.

The centre may ask questions or notify Global Pharmacovigilance Drug Safety Surveillance (DSS) Oslo that an AE report has been sent by calling +47 2318 5899 (+47 2318 5766) during office hours.

Individual case safety reports of valid serious and non-serious adverse drug reactions will be classified as solicited reports from post-marketing source. The Sponsor will report adverse drug reactions (i.e., AEs for which a causal relationship is at least a reasonable possibility) to health authorities in accordance with Regulation (EC) No. 726/2004 and Sponsor standard operating procedures (SOPs).

Causally unrelated reports of AEs will be summarised as part of any interim safety analysis and in the final study report, where applicable.

Adverse reactions to other medicines than Clariscan will be handled according to Global Pharmacovigilance SOP SPV.19.01 (Section 5.5).

Events which affect the known risk-benefit balance of Clariscan and/or impact on public health will be notified to competent authorities and the Agency, in accordance with Global Pharmacovigilance SOP SPV.19.19.

The centre should also notify the Medical Director of the SAE at one of the contact numbers below.

For any protocol or safety-related questions please contact the Medical Director:

Dr Alexis Sampedro Fromont
Senior Medical Advisor
Life Sciences
GE Healthcare
C/ Gobelas, 35-37
28023 – Madrid
Spain
T :+34 916233917
M +34 676602295
alexis.sampedro@ge.com

All AEs should be recorded using acceptable diagnoses, if possible. If an AE has already been reported it is not necessary to report each individual sign and symptom of that AE as a separate AE. For example, if myocardial infarction is reported as an AE, there is no need to report elevated creatine kinase and abnormal electrocardiogram, or other related signs, symptoms, or laboratory values as separate AEs. However, if both occurred in isolation and myocardial infarction was not diagnosed, then each event would be reported as an AE.

The intensity of all AEs will be graded as mild, moderate, or severe using the following definitions:

Mild:	Tolerable.
Moderate:	Interferes with normal activity.
Severe:	Incapacitating (causes inability to perform usual activity or work).

The investigator will be instructed to closely monitor each subject who experiences an AE (whether ascribed to the GBCA or not) until the outcome of the AE has been determined.

In addition to the investigator's own description of the AEs, each AE will be encoded by the sponsor/CRO according to a well-recognised dictionary of medical codes.

SAEs will be recorded in the eCRF if they occurred as follows:

- After a subject first received a GBCA and throughout the subject's follow-up period*, whether or not considered related to the GBCA, and
- After the subject's follow-up period, and for which a causal relationship to the GBCAs cannot be ruled out.

(*Follow-up period is defined as the protocol-stipulated period or, for subjects prematurely withdrawn from a study, the duration of a subject's participation.)

All serious and non-serious AEs must be followed for a final outcome until the end of the follow-up period. An outcome of "unknown" is not considered to be an acceptable final outcome. An outcome of "not yet resolved" is an acceptable final outcome for non-serious AEs at the end of a subject's participation in a study, and for SAEs at database lock.

10.4 Other Variables

10.4.1 Demographic Data

Subject date of birth, gender, height, weight, and BMI (calculated) will be collected.

10.4.2 Medical and Surgical History

- Medical history (including, in particular, history of allergy/asthma, eczema, renal, neurological)
- Number of previous MR, SPECT, PET, special x-ray examinations (e.g., fluoroscopy, barium studies) and CT examination for current illness/disease
- Major comorbidity and renal (level of renal impairment if know)/hepatic status
    - Renal impairment will be recorded as:

      Every effort will be made to understand the stage of renal impairment based on estimated glomerular filtration rate (eGFR). The stages of chronic kidney disease (CKD) are classified as follows:

        1. Stage 1: Kidney damage with normal or increased glomerular filtration rate (GFR; >90 mL/min/1.73 m^2)
        2. Stage 2: Mild reduction in GFR (60 to 89 mL/min/1.73 m^2)

3. Stage 3a: Moderate reduction in GFR (45 to 59 mL/min/1.73 m ^{2})
4. Stage 3b: Moderate reduction in GFR (30 to 44 mL/min/1.73 m ^{2})
5. Stage 4: Severe reduction in GFR (15 to 29 mL/min/1.73 m ^{2})
6. Stage 5: Kidney failure (GFR <15 mL/min/1.73 m ^{2} or dialysis)

Information regarding renal replacement therapy should be noted.

10.4.3 Concomitant and Concurrent Medication

Any medications taken by the subject within 24 hours of the MR examination through the end of the observation period will be recorded in the eCRF along with the indication. Either the generic or the trade name may be recorded.

10.4.4 Cumulative Data

To understand the Pattern of Use mentioned in Section 10.1, the following data will be complete only at the end of recruitment period:

- **Investigator Information (recorded once at the completion of recruitment):**

This information will be cumulative and consist of only numerical values and will include all procedures performed by the investigator regardless of whether or not the patient agreed to enrol in the study. No information about the individual patients will be required. This information will act as a denominator for calculation of percentage and proportions.

- Total number of procedure performed during the recruitment period
- Number of MRI procedures (enhanced and non-enhanced) performed during the recruitment period
- Categories/number of other procedure performed during the recruitment period

- **Centre Information (recorded once at the completion of recruitment):**

This information will be cumulative and consist of only numerical and will include all procedures performed by the investigator regardless of whether or not the patient agreed to enrol in the study. No information about the individual patients will be required. This information will act as a denominator for calculation of percentage and proportions.

- Total number of procedures performed during the recruitment period
- Categories/number of other procedure performed during the recruitment period

- Equipment for imaging (MRI, CT, ultrasound, X-ray machines, gamma camera, PET, fluoroscopy)

- Staffing of radiology department (optional)

Addition information will be recorded as categories or descriptive text (collected once at the end of recruitment period for a study centre/institution):

- Decision maker in the department – this information will be about the healthcare providers or administrator who play active role in decision making for the radiology department. For example: (categories) radiologist, head of department, cardiologist, managers, pharmacist (optional).

- Three challenges in the department in order of priority, reported as free text.

10.5 Appropriateness of Measurements

All assessments and measurements are appropriate and generally regarded as standard medical practice.

11 DATA HANDLING AND QUALITY ASSURANCE

11.1 Completing and Signing Case Report Forms

For eCRFs, data will be entered by trained site personnel with reasons given for any missing data. Any errors should be corrected within the electronic system. The audit trail will record all changes made, the date and time of the correction, and the person correcting the error. The appropriate electronic signature will be provided.

Any data recorded directly in the eCRF, for which no other written or electronic record will be maintained in the subject's medical record, will be considered source data and should be signed by the investigator(s) (e.g., results of physical examinations, vital signs testing, or the administration procedure).

11.2 Clinical Data Management

The Sponsor will be responsible for the processing and quality control of the data. Data management will be carried out by the Sponsor. The handling of data, including data quality control, will comply with all applicable regulatory guidelines.

The Stage 2 analysis (Section 10.2) will be performed at a later date and will not be part of the initial read out of the study. The images for the Stage 2 analysis will be selected and transferred via AGMednet to the Sponsor at the end of the recruitment period and will be archived for later use. Stage 2 blinded image evaluation results will be collected in a database that is separate from the database utilised for the Stage 1 analysis, and will not prohibit the procedures for locking and analysing the database for the Stage 1 analysis. No changes to the Stage 1 data will be made after the database is locked. Stage 1 and Stage 2 data will be merged after the blinded image evaluation is conducted for separate analysis.

11.3 Archiving

All study documentation at the investigator site and sponsor site will be archived in accordance with International Conference on Harmonisation (ICH) E6-Good Clinical Practice (GCP) and the CRO's quality standards and SOPs.

All study documentation at the investigator site and sponsor site will be archived for a minimum of 15 years following completion or discontinuation of the study, unless notified otherwise by the Sponsor or a longer period is required by local legislation. The investigator must request written agreement from the sponsor before destruction of archived study documentation.

12 STATISTICAL METHODS AND PLANNED ANALYSIS

The data will be analysed by the CRO. Any data analysis carried out independently by the investigator should be submitted to the sponsor before publication or presentation.

Data from participating centres in this protocol will be combined so that an adequate number of subjects will be available for analysis. The data will be summarised with respect to demographic and baseline characteristics, efficacy observations and measurements, safety observations and measurements.

12.1 General Statistical Considerations

Tabulations of summary statistics, graphical presentations, and statistical analyses will be performed using SAS® software, Version 9.3 or higher. Descriptive statistics for continuous data in summary tables will include the number of subjects in the analysis (n), mean, standard deviation, median, and range (minimum, maximum). Descriptive statistics for categorical data in summary tables will include counts and percentages. All data obtained on the eCRF and entered into the database will be provided in separate data listings showing individual subject values. The planning and reporting of statistical analysis will be carried out as described in the CRO's SOPs governing clinical studies.

12.2 Populations for Analysis

Full Analysis Set

The Full Analysis Set will include all enrolled patients who signed the informed consent.

Effectiveness Analysis Set

The Effectiveness Analysis Set will include all patients who received a GBCA and underwent an MR examination.

Safety Analysis Set

The Safety Analysis Set will consist of all patients who received GBCA during the study.

Investigator Analysis Set

The Investigator Analysis Set will include all investigators who performed at least one GBCA-enhanced MR procedure as part of this study.

Centre Analysis Set

The Centre Analysis Set will include all centres that were approved and initiated to take part in this study and performed at least one GBCA-enhanced MR procedure as part of this study.

12.3 Subject Demographics/Other Baseline Characteristics

A table will be provided with the following patient-level information:

- Number of subjects enrolled (full analysis set).
- Number of subjects included in the effectiveness analysis.
- Number of subjects included in the safety analysis.
- Number of subjects withdrawn from the study and the reason for withdrawal.

Demographic information (age, height, weight, and BMI will be summarised using descriptive statistics. Gender and race will be summarised by counts and percentages.

Baseline characteristics such as the number of previous MR, SPECT, PET, special x- ray examinations (e.g., fluoroscopy, barium studies) and CT examination for current illness/disease, hepatic status, and renal status will be summarised.

Medical histories and concomitant medications will be summarised by counts and percentages.

12.4 Study Treatments

Study treatment will be administered according to clinical practice. The dose administered will be summarised by type and volume of GBCA as well as the volume of saline.

12.5 Pattern of Use Analyses

The pattern of use for GBCAs for MR (MRA/MRI) examination will be summarised for all GBCAs pooled, for non-Clariscan GBCAs pooled, and for all individual GBCAs administered during the study, including Clariscan. The overall pattern of use will be assessed based on summary data from a number of different centre, investigator, and patient-level variables as outlined below.

A qualitative analysis of these variables will be performed describing the overall pattern of use, referral pattern, and challenges in a radiological practice.

12.5.1 Centre Variables

The following summaries will be provided for the Centre Analysis Set:

- The average number of radiological procedures performed overall by centres during the recruitment period of the study.

- The average number of each type or radiological procedure (ultrasound, MR, CT scan, fluoroscopy, X-ray, SPECT, and PET examinations) performed by centres during the recruitment period of the study.

- The average percentage of each type of radiological procedure performed by centres during the recruitment period of the study as a proportion of the overall number of radiological procedures performed during the same period. The overall number of procedures from the centre will act as a denominator for the calculation of percentage and proportions of individual types of procedures.

- The average number of MR machines and staff (nurses and technicians) utilised by centres during the recruitment period of the study.

12.5.2 Investigator Variables

The following summaries will be provided for the Investigator Analysis Set:

- The average number of radiological procedures performed overall by investigators during the recruitment period of the study.

- The average number of each type or radiological procedure (ultrasound, MR, CT scan, fluoroscopy, X-ray, SPECT, and PET examinations) performed by investigators during the recruitment period of the study.

- The average percentage of each type of radiological procedure performed by investigators during the recruitment period of the study as a proportion of the overall number of radiological procedures performed during the same period. The overall number of procedures from the centre will act as a denominator for the calculation of percentage and proportions of individual types of procedures.

- The average number of enhanced and non-enhanced procedures performed by investigators during the recruitment period of the study.

12.5.3 Patient-Level Variables

The following summaries will be provided for the Full Analysis Set:

- The number of times a GBCA was used per indication, organ/system imaged, age, gender, BMI, reason for use of GBCA and preference for a particular GBCA based on BMI.

- The number of each type of referring physician (seniority or specialty).

- The quality of the referral during the recruitment period of the study.

- The number of repeat MR examinations that are performed during the recruitment period of the study and a summary of the reasons for repeat exams.

12.6 Effectiveness Variables and Analyses

Effectiveness data will be summarised for all GBCAs pooled, for non-Clariscan GBCAs pooled, and for all individual GBCAs administered during the study, including Clariscan. Statistical differences in image quality and diagnostic confidence between groups (Clariscan vs non-Clariscan GBCAs pooled and Clariscan vs each individual GBCA) will be assessed at an alpha of 0.05. However, no formal statistical hypotheses will be tested and no adjustments will be made for multiplicity.

The following summaries will be provided for the Effectiveness Analysis Set:

- The average image quality.
- The average change in diagnostic confidence (diagnostic confidence using CE-MR enhanced image minus diagnostic confidence using the non-enhanced image).
- The proportion of patients for whom contrast-enhanced MRI changed the diagnosis (asked as a yes/no question on the eCRF).
- The proportion of patients for whom contrast-enhanced MRI increased the confidence in diagnosis (asked as a yes/no question on the eCRF).

Stage 2 analyses (Section 10.2) will be conducted at a later date and will be outlined in a separate analysis plan.

12.7 Safety Variables and Analyses

12.7.1.1 Adverse Events

AEs will be summarised for all GBCAs pooled, for non-Clariscan GBCAs pooled, and for all individual GBCAs administered during the study, including Clariscan. AEs and SAEs will be coded using Medical Dictionary for Regulatory Activities (MedDRA) and all reported events will be listed for the Safety Analysis Set. Immediate treatment-emergent AEs (TEAE) are defined as AEs that occur from the time of treatment administration through 1 hour after administration. Delayed TEAEs are defined as AEs that occur later than 1 hour post-administration up to 7 days post-administration.

The number and percentage of patients with 1 or more AEs will be summarised by system organ class and preferred term. Summaries will also be presented by AE intensity and judged relationship to study drug. Treatment-emergent SAEs will be presented by treatment group for the safety population.

12.8 Interim Analysis

No interim analyses are planned for this study.

12.9 Sample Size Calculation

This is an observational study to understand the pattern of use of GBCAs use in CE-MR. The sample size is not based on statistical considerations, as the study does not formally test a hypothesis. Recruitment will be open for 3 months (90 days), with a cap on the maximum number of patients recruited by each centre (Table 1), and all consecutive patients who provide informed consent from the start of study (after Clariscan is on formulary in the study centre and available for routine clinical use) will be enrolled. Even if the centre has not enrolled the maximum number of patients allocated for that centre, recruitment will close at the end of the 90-day enrolment period regardless of the number of patients enrolled. It is anticipated that up to 5,400 patients from European countries where Clariscan has been launched will be enrolled. The maximum number of patients per country can be found in Table 1.

12.10 Procedures for Missing, Unused and Spurious Data

Missing values will not be substituted by estimated values, but treated as missing in the statistical evaluation. All data from all subjects dosed in the study will be included in all listings, plots, summary tables, and statistical analyses when appropriate.

12.11 Rules for Excluding Subjects from Analysis

All dosed subjects will be included in the analyses unless otherwise specified. The sponsor will make any decisions regarding whether any subjects or any individual values belonging to a subject will be excluded from the evaluations when the protocol violation is considered to have a negative impact on the scientific aspects and interpretation of the study results. Such judgments should be made in a blinded fashion before database lock and before any analyses have been performed. If the subject has received any GBCA, all available safety data will be used. The reason(s) for any exclusion will be described in the report.

12.12 Procedures for Reporting Deviations from Original Statistical Plan

Any deviations from the statistical analysis outlined in this protocol will be described, and reasons for the deviations listed, in the final Clinical Study Report.

13 SPECIAL REQUIREMENTS AND PROCEDURES

13.1 Regulatory, Institutional, and Ethical Review

Before starting this study, the protocol (authorised by the sponsor) will be submitted to the regulatory bodies/local health authorities (in accordance with local regulations) and to the Independent Ethics Committee (IEC) for evaluation. The protocol will also be signed by the principal investigator before submission to the IEC. The study will not start before the IEC gives written approval or a favourable opinion in accordance with ICH E6-GCP and all applicable regulatory bodies/local health authorities give approval or a favourable opinion as required.

No changes from the final approved (authorised) protocol will be initiated without the IEC's prior written approval or favourable opinion of a written amendment, except when necessary to eliminate immediate hazards to the subjects or when the change involves only logistics or administration. The sponsor will authorise and the principal investigator(s) will sign the protocol amendment prior to submission to the IEC. Protocol amendments should be submitted to the IEC without delay.

13.2 Ethical Considerations

Where IEC/Competent Authorities (CA) approval is required, the study can only begin after acquisition of a written approval/favourable opinion from the Committee/Authority. Where applicable, the approval/favourable opinion will contain:

- Identity of the study
- Date of review
- Documents reviewed
- List of names, titles and professions of the committee in the case of IEC favourable opinion

The original or copy of the approval/favourable opinion should be submitted to the Sponsor or Sponsor's designee.

The Investigator should submit accurate and adequate reports to the IEC/CA within the timelines as per local and national requirements.

13.3 Investigator's Responsibilities

13.3.1 Overall Responsibilities

The investigator(s) is/are responsible for conducting the study in full accordance with the Protocol and the Declaration of Helsinki, the *Good Clinical Practice: Consolidated Guideline*, approved by the ICH, and any applicable national and local laws and regulations. Information regarding any investigational centres participating in this study that cannot comply with these standards will be documented.

13.3.2 Subject Informed Consent

Written and oral information about the study in a language understandable by the subject will be given to all subjects. Each subject's willingness to participate in the study will be documented in a signed and dated informed consent form before any procedures or assessments are done and after the aims, methods, anticipated benefits, potential hazards, and insurance arrangements in force are explained. It will also be explained to the subjects that they are free to refuse entry into the study and free to withdraw from the study at any time without prejudice to future treatment. The informed consent process will be documented in the subject's medical record and the investigator will sign, date and time the informed consent form after the subject has signed, dated and recorded the time. The investigator(s) will keep the original consent forms and copies will be given to the subjects.

13.3.3 Direct Access to Source Data/Documents

The monitor(s), auditor(s), authorised personnel of the Sponsor/CRO, health authority inspector(s) or their agents, and authorised members of IECs will be given direct access to source data and documentation (e.g., medical charts/records, laboratory results, printouts, videotapes, etc.) for source data verification, provided that subject confidentiality is maintained in accordance with local requirements.

13.3.4 Confidentiality Regarding Study Subjects

The investigator(s) must assure that the privacy of the subjects, including their personal identity and all other personal medical information, will be maintained at all times. In eCRFs and other documents or image material (including materials from all examinations, e.g., CT, MR, CT, fluoroscopy, X-ray, SPECT, PET) submitted to the sponsor/CRO, subjects will not be identified by their names, but by an identification code (e.g., study subject number).

Personal medical information may be scrutinised for the purpose of verifying data recorded in the eCRF. This may be done by the monitor(s), properly authorised persons on behalf of the sponsor, the quality assurance unit, or regulatory authorities. Personal medical information will always be treated as confidential.

13.4 Protocol Deviations

Any deviation from the protocol when no approved amendment exists must be documented as a protocol deviation and reported according to local requirements. If appropriate, corrective and preventative action must be implemented to avoid repetition. Protocol deviations and any potential impact on the study results will be discussed during the reporting of the study.

Waivers or protocol exceptions will not be granted prospectively by the Sponsor under any circumstances.

13.5 Study Monitoring

Study monitoring will be performed in accordance with ICH E6-GCP, the Sponsor/CRO SOPs, the protocol, and applicable local regulations.

13.6 Audit and Inspection

According to ICH E6-GCP, the sponsor or regulatory authorities may audit the investigational site. The Sponsor's Quality Assurance Unit, independent of the Clinical Research and Development Department, is responsible for auditing the study.

The investigator(s) must accept that regulatory authorities may conduct an inspection to verify compliance of the study with GCP.

13.7 Insurance

This study is covered under the sponsor's Liability Insurance Policy (under General Electric Insurance Company and/or a company designated by the study sponsor). A Certificate of Insurance and/or an information leaflet containing essential information about the insurance coverage can be provided upon request.

13.8 Publication Policy

The investigator and/or Institution shall have the right to publish the results of their work conducted under this protocol, subject to providing the sponsor with the opportunity to review the contents of any proposed abstract or publication concerning the work, including any results of the study, in advance of publication and if necessary to delay publication for a limited time not to exceed 60 days in order to protect the confidentiality or proprietary nature of any information contained therein. The sponsor will make every reasonable effort to consider and release each proposed publication within 30 days, or proposed abstract within 15 days, of submission.

14 REFERENCES

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Hansmann J, Michaely HJ, Morelli JN, Luckscheiter A, Schoenberg SO, Attenberger UI. Enhancement Characteristics and Impact on Image Quality of Two Gadolinium Chelates at Equimolar Doses for Time-Resolved 3-Tesla MR-Angiography of the Calf Station. PLOS ONE. 2014 June;9(6):e99079.

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Maravilla KR, San-Juan D, Kim SJ, Elizondo-Riojas G, Fink JR, Escobar W, et al. Comparison of Gadoterate Meglumine and Gadobutrol in the MRI Diagnosis of Primary Brain Tumors: A Double-Blind Randomized Controlled Intraindividual Crossover Study (the REMIND Study). AJNR Am J Neuroradiol. 2017 June 29. doi: 10-3174/ajnr.A5316. [Epub ahead of print].

15 APPENDICES

15.1 Information on Investigational and Registered Products

The reference document for this study is the current SPC. The reference document provides up-to-date information on the efficacy and safety of Clariscan, and is used for assessing expectedness of serious adverse drug reactions, in order to determine regulatory reportability. An unexpected adverse drug reaction is a reaction, for which the nature, seriousness, severity or outcome is not consistent with the applicable product information, e.g., the SPC for the study drug.

15.2 Radiological Definitions and Classification of Adverse Events

Reference: [ESUR Guidelines 2017]

ACUTE ADVERSE REACTIONS

Definition: An adverse reaction which occurs within 1 hour of contrast medium injection.

The same acute adverse reactions are seen after iodine- and gadolinium-based contrast agents and after ultrasound contrast agents. The incidence is highest after iodine-based contrast agents and lowest after ultrasound agents.

Classification

Acute reactions are either allergy-like, hypersensitivity reactions or chemotoxic responses. Allergy-like reactions may or may not be true IgE-mediated allergy.

	Allergy-like/ Hypersensitivity	**Chemotoxic**
Mild	Mild urticaria Mild itching Erythema	Nausea/mild vomiting Warmth/chills Anxiety Vasovagal reaction which resolves spontaneously
Moderate	Marked urticaria Mild bronchospasm Facial/laryngeal oedema Vomiting	Severe vomiting Vasovagal attack
Severe	Hypotensive shock Respiratory arrest Cardiac arrest	Arrhythmia Convulsion

Note:

- Not all symptoms experienced by patients in the hour after contrast medium injection are adverse reactions to the contrast agent.
- Patient anxiety may cause symptoms after contrast medium administration (Lalli effect).
- When a new contrast medium is first introduced, adverse effects tend to be over-reported (Weber effect).

A.1.4. RECORDING ACUTE ADVERSE REACTIONS

- Acute adverse reactions must be properly documented in the patient's records, so that appropriate precautions can be taken before any future examination.
- All reactions requiring medical treatment should be recorded.
- Mild symptoms after contrast medium not requiring treatment should not be recorded. They may be unrelated to the contrast medium and caused by anxiety or by the patient's disease. If such minor symptoms are recorded, the patient may in future be denied a clinically important enhanced examination.
- Full documentation of acute allergy-like reactions includes (a) measuring serum tryptase, preferably immediately after and 2 hours after the reaction, and (b) skin testing one month after the reaction to check for evidence of true allergy to the triggering contrast agent and for evidence of cross-reactivity to other agents.

LATE ADVERSE REACTIONS

Definition:	A late adverse reaction to intravascular iodine-based contrast medium is defined as a reaction which occurs 1 hour to 1 week after contrast medium injection.
Reactions:	Skin reactions similar in type to other drug-induced eruptions. Maculopapular rashes, erythema, swelling and pruritus are most common. Most skin reactions are mild to moderate and self-limiting. A variety of late symptoms (e.g., nausea, vomiting, headache, musculoskeletal pains, fever) have been described following contrast medium, but many are not related to the contrast medium.
Risk factors for skin reactions:	Previous late contrast medium reaction. Interleukin-2 treatment. Use of non-ionic dimers.
Management:	Symptomatic and similar to the management of other drug-induced skin reactions, e.g., antihistamines, topical steroids and emollients.
Recommendations:	Patients who have had a previous contrast medium reaction, or who are on interleukin-2 treatment should be advised that a late skin reaction is possible and that they should contact a doctor if they have a problem. Patch and delayed reading intradermal tests may be useful to confirm a late skin reaction to contrast medium and to study cross-reactivity patterns with other agents. To reduce the risk of repeat reaction, use another contrast agent than the agent precipitating the first reaction. Avoid agents which have shown cross-reactivity on skin testing. Drug prophylaxis is generally not recommended.

Note: Late skin reactions of the type which occur after iodine-based contrast media have not been described after gadolinium-based and ultrasound contrast media. **However, the Clariscan SPC does mention delayed reactions after one hour to few days' time.**