GE Healthcare

Clinical Study Protocol

Use of Digital Tomosynthesis for Detection and Case Management of Scaphoid and Distal Radius Fractures: A VolumeRAD Data Collection Study

(STUDY NO.124.02-2018-GES-0001)

Version: 2.0; 24/Oct/2018

Sponsor: General Electric Company, acting through its GE Healthcare Business
3000 N. Grandview Blvd
Waukesha, WI 53005

Investigational Device/Product: VolumeRAD

Modality: Detection and Guidance Solutions (DGS) - X-Ray

FOR QUALIFIED INVESTIGATORS, STUDY STAFF, AND THEIR ETHICS COMMITTEE(S) ONLY

CONFIDENTIALITY STATEMENT

Information in this RESEARCH STUDY PROTOCOL is for investigators, site personnel involved with the study, ethics committee(s), and/or their authorized representative(s) except as required to obtain consent from study participants or as otherwise required by law. Once signed, the terms of the protocol are binding for all parties.

The Sponsor and Principal Investigator have approved this protocol version, and I confirm hereby to conduct the study according to the protocol and in accordance with applicable principles of the World Medical Association Declaration of Helsinki and Good Clinical Practice (GCP) guidelines as per ISO 14155:2011, any conditions of approval imposed by the reviewing EC or governing regulatory body, and applicable laws and regulations. The PI should not deviate from this protocol except for emergency use. I have read and understood and agree to abide by all the conditions and instructions contained in this protocol.

Local Principal Investigator at study site:

Investigator Signature	Date
Print Name	
Site Name, Department, Address	

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DOCUMENT AND VERSION CONTROL

This section records all changes made to the protocol for a specific study. In the table below, record every relevant change by indicating what changes were made.

Revision	Date (DD/Mmm/YYYY)	Revision Author	Comments/Changes
1.0	28/Jun/2018	Aneysha Bhat	Clinical Writer – This is the initial version.
2.0	24/Oct/2018	Aneysha Bhat	Clinical Writer – Revised device risk and safety information, as described in Appendix B – Amendments (Protocol Version 1.0 to 2.0).

LIST OF ABBREVIATIONS AND TERMS

3D	Three Dimensional
AE	Adverse Event
ADE	Adverse Device Effect
ALARP	As Low as Reasonably Practicable
AMA	American Medical Association
BS	Bone scintigraphy
CAPM	GE Clinical Affairs Project Manager
CCG	Case Report Form Completion Guidelines
CFR	Code of Federal Regulations
CHF	Clinical History File (synonymous with e-Trial Master File)
CRF	Case Report Form
CT	Computed Tomography
DTS	Digital Tomosynthesis
DCF	Data Clarification Form
EC	Ethics Committee
EU	European Union
FDA	United States Food and Drug Administration
GCP	Good Clinical Practice (see ISO 14155:2011) [1]
GE	General Electric
GEHC	General Electric Healthcare
ICF	Informed Consent Form
ISO	International Standards Organization
IRB	Institutional Review Board
ORIF	Open Reduction Internal Fixation
MRI	Magnetic Resonance Imaging
MWS	GE MyWorkshop Internal Documentation System
PI	Principal Investigator
SADE	Serious Adverse Device Effect
SAE	Serious Adverse Event
SOC	Standard of Care
SPR	System Problem Report
US	United States
USADE	Unexpected Serious Adverse Device Effect
XR	X-Ray

STUDY SYNOPSIS

Sponsor:	General Electric Company, acting through its GE Healthcare Business
Research Type:	This is a clinical, open-label, prospective research study conducted at up to two (2) sites in the United States (US).
Regulatory Status:	This is a post-market research study of the following devices/products: *Pre-market*: None *Post-market*: VolumeRAD
Background and Study Purpose:	The purpose of this study is to support additional, on-label claims for GE Healthcare (GEHC) X-ray's VolumeRAD advanced application. This study is designed to support the FDA 510(k) claims that VolumeRAD is superior to conventional X-ray in the detection and treatment of distal radius and scaphoid wrist fractures.
Objectives:	**Primary Objective:** The primary objective of this study is to collect image and technical data on routine X-ray, DTS, and CT (or MRI) imaging modalities. **Secondary Objective:** The secondary objective is to collect per-subject data including diagnosis and treatment information. **Safety Objective:** The safety objective is to collect safety information, including type and number of AEs, SAEs, and device issues.
Endpoints:	**Primary Endpoint:** The primary endpoint is the collection of image sets from X-ray, DTS, and CT (or MRI) imaging exams for each complete and evaluable subject case. **Secondary Endpoint:** The secondary endpoint is the collection of subject diagnosis and treatment information, including de-identified radiologist and surgical reports (which will be the truth status for all data collected), for each complete and evaluable subject case. **Safety Endpoint:** The safety objective is to collect safety information, including type and number of AEs, SAEs, and device issues.

<table>
<tr><td>Procedures/
Methods:</td><td colspan="2">Control-arm: Following subject enrollment and consent, control-arm subjects will undergo study-related X-ray imaging and DTS imaging. Imaging results and de-identified radiologist reports will be collected and recorded.

Test-arm: Eligible subjects shall consist of patients presenting with a wrist injury. The patients shall undergo initial X-ray imaging per standard of care (SOC) at the site. If the initial X-ray imaging shows a suspected or confirmed distal radius or scaphoid wrist fracture, additional imaging, including DTS and/or CT and/or MRI, shall be ordered.

The patient may undergo DTS imaging per site SOC. The subject shall then undergo CT or MRI imaging. The point of enrollment in the study will be the completion of informed consent prior to or immediately after the completion of the SOC CT or MRI exam. The SOC X-ray and/or DTS imaging data shall be collected retroactively from these subjects.

After SOC imaging has been completed, study-specific DTS shall be completed for subjects who have not previously completed SOC DTS imaging.

Subjects shall receive treatment as needed. Diagnostic truth and treatment truth will be collected and recorded on a per-subject basis. De-identified radiologist and surgical reports will be collected for each subject.</td></tr>
<tr><td>Eligibility criteria for Test-arm Subjects:</td><td>Inclusion criteria:
Subjects who meet all of the following inclusion criteria may be included in this study:
1) Are adults aged 18 years or older;
2) Have a confirmed or suspected distal radius or scaphoid wrist fracture;
3) Have completed an X-ray imaging exam per standard of care;
4) Have a standard of care CT or MRI exam ordered;
5) Are able and willing to complete DTS imaging exam (if not already completed);
6) Are able and willing to comply with study procedures; and
7) Are able and willing to provide written informed consent to participate in this study.</td><td>Exclusion criteria:
Subjects who meet any of the following exclusion criteria will be excluded from this study:
1) Are documented as pregnant based on PI’s medical judgment and in consideration of local clinical practice standards for evidence of pregnancy;
2) Have additional trauma within the image field of view that either impacts the visualization or changes the treatment of the scaphoid or distal radius fracture;
3) Have had prior reconstructive surgery or fixation in the wrist.</td></tr>
</table>

Eligibility criteria for Control-arm Subjects:	**Inclusion criteria:** Subjects who meet all of the following inclusion criteria may be included in this study: 1) Are adults aged 18 years or older; 2) Are able and willing to comply with study procedures; and 3) Are able and willing to provide written informed consent to participate in this study.	**Exclusion criteria:** Subjects who meet any of the following exclusion criteria will be excluded from this study: 1) Are documented as pregnant based on PI's medical judgment and in consideration of local clinical practice standards for evidence of pregnancy; 2) Have had known prior trauma in either wrist.
Sample size and Sites:	Up to 140 subjects shall be enrolled in this study from up to two (2) sites, including up to 50 subjects presenting suspected or confirmed scaphoid wrist fractures and up to 50 subjects presenting suspected or confirmed distal radius wrist fractures to achieve a target of at least 31 evaluable subjects in each of these two categories. Up to 40 healthy volunteers will be enrolled to achieve a target of at least 25 normal image sets for collection in this study. Subjects who shall have 'completed' the study are defined as 1) subjects who have complete image sets available from X-ray (as per Standard of Care), Digital Tomosynthesis (DTS) (either SOC or research order), and CT or MRI (test-arm subjects); 2) have diagnostic truth known and available; and 3) have treatment truth known and available.	
Study duration:	The expected study duration is approximately one year.	

ADMINISTRATIVE STRUCTURE OF INVESTIGATION

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1. BACKGROUND AND JUSTIFICATION

Wrist radius fractures are one of the most common types of fractures, accounting for around 25% of fractures in the pediatric population and up to 18% of all fractures in the elderly age group. Current and past clinical data point to a rise in the incidence of distal radius fractures for the pediatric, adult, and elderly populations in recent years.[2]

When a patient presents to the emergency department with a wrist injury and clinical signs of a scaphoid fracture, initial radiographs include detection of fractures. Approximately 20% of them do have a true scaphoid fracture and need additional imaging to establish a definitive diagnosis. However, due to the low healing potential of the scaphoid bone, adequate diagnosis and treatment is essential in order to prevent complications such as non-union, i.e. a fractured bone failing to heal after an extended period of recovery. If a patient is clinically suspected for a scaphoid fracture, their wrist will be immobilized in a cast until definitive diagnosis is obtained. This fear of under-treatment results in a large amount of over-treated wrist injuries.[3]

X-ray is the most commonly used imaging tool in fractures; despite being a basic imaging tool, X-ray provides less sensitivity and accuracy than other imaging modalities such as MRI or CT, as stress or non-displaced fractures are commonly missed in plain radiographs. Computed tomography (CT) and magnetic resonance imaging (MRI) are two imaging modalities that can be used at this stage in the primary evaluation of a suspected wrist fracture as well as the assessment of bone healing after the fracture.[4] However, these imaging modalities have several disadvantages, including metal artifacts, increased radiation exposure, and higher costs. [2,3,5]

Digital Tomosynthesis (DTS) is an application that uses the X-ray system to take high-resolution, low-dose projection image slices during a single sweeping motion of the X-ray tube over a limited angle. A computer then assembles this information to provide up to 60 high-resolution slice images available in a three-dimensional (3D) viewing capacity.[2,3] For orthopedic imaging applications, DTS has been reported to be advantageous for improved imaging of complex anatomic structures, subtle fractures, and articular surfaces of joints compared with conventional radiography. Compared with conventional radiography, DTS allows for easier detection of fractures, and can even demonstrate occult fractures not visible with conventional radiography, with less tissue overlap, better anatomic visualization, less dependence on the technical skill of the radiographers, and reduced need for painful patient positioning or multiple projections of different views in patients with suspected fractures of fine and complex osseous structures.[6] GE Healthcare's VolumeRAD application uses DTS to provide additional clinical information to radiologists necessary for optimal diagnosis and treatment purposes.

The study described herein is being conducted to collect clinical data associated with diagnosis and treatment information to support additional, on-label claims for GEHC's VolumeRAD advanced application. The results of this study are intended for use in the submission of FDA 510(k) claims in the United States. Results may be used by the Sponsor in future investigations, engineering, and regulatory purposes.

2. DEVICE DESCRIPTION

2.1 Identity, Mechanism, and Function

Name: VolumeRAD

Modality/Type: Detection and Guidance Solutions (DGS)

Manufacturer: GE

Regulatory Status: Post-market

Note: A record of number of devices issued, along with applicable identification numbers (e.g. serial/lot/batch) and components/accessories used in this study will be retained by the Sponsor as part of the clinical history file (CHF), as required by applicable laws and regulations.

VolumeRAD is a digital tomosynthesis (DTS) feature (FDA 510(k): K132261) manufactured by GE Healthcare (GEHC). VolumeRAD is an X-ray system capable of generating radiographic and tomographic images of human anatomy.

VolumeRAD provides multiple images of human anatomy in a single sweeping motion using a low radiation dose. During the sweep, up to 60 ultra-low dose exposures are obtained. Similar to CT exams, the acquired data is reconstructed into a set of tomographic images. These images, in DICOM format, can be reviewed sequentially on the acquisition console or on any standard review workstation.

The research device, instructions for use, or packaging shall indicate that the research device is for use in a research investigation, in accordance with applicable regulations in the United States (US) and other applicable laws and regulations.

Results may be used by the Sponsor in future investigations, engineering, and regulatory purposes.

2.2 Intended Use

VolumeRAD is intended to be used to generate tomographic images of human anatomy including the skull, spinal column, chest, abdomen, extremities, and other body parts in patients of all ages. VolumeRAD is not intended for mammographic applications.

The procedures conducted in this study are intended for research purposes and are not intended as a substitute for required medical care.

2.3 Reference Standard

There is no reference device being used in this data collection study.

2.4 Concomitant/Ancillary Administrations

2.4.1 Medications and Biologic Products

No medications or biologic products will be administered as part of study procedures.

2.4.2 Laboratory Tests and Sample Processing

No laboratory tests or sample processing is planned as part of the study procedures.

2.5 Accountability

Devices used in this study will be site-owned. Accurate and adequate records will be maintained for all devices being used in this study. The Principal Investigator (PI) will be ultimately responsible for the security and integrity of research devices/products at the investigational site during the course of the study.

2.5.1 Issuance and Disposition

The VolumeRAD DTS device used in this study will be site-owned.

2.6 Anticipated Risks and Benefits

The device/product under study has undergone risk assessment, in accordance with International Standards Organization (ISO) 14971:2012. Risks have been mitigated to levels as low as reasonably practicable (ALARP) and are not expected to exceed risks associated with routine X-ray procedures as conducted in standard clinical practice.

The risks of study participation are not expected to be greater than those of similar procedures routinely conducted in clinical practice. Follow-up shall be conducted as needed on a per-subject basis per site standard of care.

There are no expected risks to subjects, operators, or others in this study beyond those of routine/similar devices/products in clinical care.

Subjects are not expected to benefit directly from study participation. The results may benefit future patients by increasing knowledge about the use of VolumeRAD in clinical settings.

2.6.1 Risk Category and Rationale

VolumeRAD is classified as a Class II medical device. As used in this study, it is not considered a significant risk device per the 21 CFR §812.3 definition:

1) it is not intended as an implant;
2) is not purported or represented to be for a use in supporting or sustaining human life;
3) is not for a use of substantial importance in diagnosing, curing, mitigating, or treating disease, or otherwise preventing impairment of human health;
4) and it does not otherwise present a potential for serious risk to the health, safety, or welfare of a subject.

3. STUDY OBJECTIVES AND ENDPOINTS

3.1 Purpose of the Study

The purpose of the study is to collect clinical data associated with diagnostic and treatment information to support additional, on-label claims for GEHC's X-ray VolumeRAD advanced application.

3.1.1 Primary Objective:

The primary objective of this study is to collect image and technical data on routine X-ray, DTS, and CT (or MRI) imaging modalities.

3.1.2 Secondary Objective(s):

The secondary objective is to collect per-subject data including diagnosis and treatment information.

3.1.3 Safety Objective(s):

The safety objective is to collect safety information, including type and number of AEs, SAEs, and device issues.

3.2 Study Endpoints

3.2.1 Primary Endpoints:

The primary endpoint is the collection of image sets from X-ray, DTS, and CT (or MRI) imaging exams for each complete and evaluable subject case.

3.2.2 Secondary Endpoints:

The secondary endpoint is the collection of subject diagnosis and treatment information, including de-identified radiologist and surgical reports (which will be the truth status for all data collected), for each complete and evaluable subject case.

3.2.3 Safety Endpoints

The safety endpoint will be the type and number of AEs, SAEs, and device issues.

4. STUDY DESIGN

This is a post-market, open-label prospective clinical research study conducted at up to two (2) sites in the United States (US).

4.1 Study Population

Eligible test subjects shall be subjects ≥ eighteen (18) years who are presenting with a suspected or confirmed distal radius or scaphoid wrist fracture and are clinically indicated for advanced imaging.

4.2 Number of Subjects

Up to 140 subjects shall be enrolled in this study from up to two (2) sites, including up to 50 subjects presenting suspected or confirmed scaphoid wrist fractures and up to 50 subjects presenting suspected or confirmed distal radius wrist fractures to achieve a target of at least 31 evaluable subjects in each of these two categories. Up to 40 healthy volunteers will be enrolled to achieve a target of at least 25 normal image sets for collection in this study. In this study, the term “normal” will refer to any non-fracture positive images from any subjects in the control-arm of the study (i.e. healthy volunteers).

There will be two groups of subjects in this study – the test-arm group and the control-arm group.

The control-arm group will consist of healthy volunteers with no known prior trauma in the wrists. The diagnostic truth for subjects in the control-arm will be no fracture and the treatment truth will be no treatment.

The test-arm group will consist of subjects who present with a wrist injury and initial SOC X-ray imaging results show a confirmed or suspected distal radius or scaphoid fracture, for which additional diagnostic imaging shall be ordered. Diagnostic truth for subjects in the test-arm will be the per-subject clinical diagnosis and the treatment truth will be the per-subject treatment received.

Subjects who shall have completed the study are defined as 1) subjects who have complete image sets available from X-ray (per standard of care [SOC]), DTS (either SOC or research ordered), and CT or MRI (test-arm subjects); 2) have diagnostic truth known and available; and 3) have treatment truth known and available.

4.3 Protection of Vulnerable Subjects

Vulnerable subjects are individuals whose willingness to volunteer in a clinical investigation could be unduly influenced by the expectation, whether justified or not, of benefits associated with participation or of retaliatory response from senior members of a hierarchy in case of refusal to participate.

The Sponsor shall avoid improper influence on, or inducement of, the subject, monitor, any investigator(s), or other parties participating in, or contributing to, the clinical investigation.

All investigators shall avoid improper influence on, or inducement of, the subject, Sponsor, monitor, other investigator(s), or other parties participating in, or contributing to, the clinical investigation.

This study does not examine any groups of subjects who are considered to be vulnerable subjects in the country in which the study is being conducted.

4.4 Eligibility Criteria for Test-arm Subjects

4.4.1 Inclusion Criteria

Subjects who meet all of the following inclusion criteria may be enrolled in this study:

1) Are adults aged 18 years or older;
2) Have a confirmed or suspected distal radius or scaphoid wrist fracture;
3) Have completed an X-ray imaging exam per standard of care;
4) Have a standard of care (SOC) CT or MRI exam ordered;
5) Are able and willing to complete DTS imaging exam (if not already completed);
6) Are able and willing to comply with study procedures; and
7) Are able and willing to provide written informed consent to participate in this study.

4.4.2 Exclusion Criteria

Subjects who meet any of the following exclusion criteria will be excluded from this study:

1) Are documented as pregnant based on PI's medical judgment and in consideration of local clinical practice standards for evidence of pregnancy;
2) Have additional trauma within the image field of view that either impacts the visualization or changes the treatment of the scaphoid or distal radius fracture;
3) Have had prior reconstructive surgery or fixation in the wrist.

4.5 Eligibility Criteria for Control-arm Subjects

4.5.1 Inclusion Criteria

Subjects who meet all of the following inclusion criteria may be enrolled in this study:

1) Are adults aged 18 years or older;
2) Are able and willing to comply with study procedures; and
3) Are able and willing to provide written informed consent to participate in this study.

4.5.2 Exclusion Criteria

Subjects who meet any of the following exclusion criteria will be excluded from this study:

1) Are documented as pregnant based on PI's medical judgment and in consideration of local clinical practice standards for evidence of pregnancy;
2) Have had known prior trauma in either wrist.

4.6 Controls and Minimization of Bias

The following bias control methods shall be employed in this study:

- Selection bias will be limited by consecutively enrolling eligible subjects.
- Spectrum bias will be limited by using a population expected to represent the general population at the site(s).

4.7 Recruiting and Screening

Subjects in both groups of the study will be recruited for potential enrollment in this study according to the standard procedures of the site, unless otherwise specified by the Sponsor in this study protocol.

Subjects in both groups of the study will be screened for enrollment in this study against the inclusion and exclusion criteria according to the standard procedures of the site. Enrollment determinations will be made by the PI. All subject participation will be voluntary.

4.7.1 Enrollment of Test-arm Subjects

Patients who have SOC X-ray for a wrist injury and who have been referred for a SOC CT or MRI, shall be recruited.

The subject shall be considered enrolled (the point of enrollment) once he/she signs and dates the informed consent form (ICF) prior to or immediately after completion of the SOC MRI or CT exam.

Once enrolled, the subject will be assigned a unique subject number, which will not contain information that could identify the subject (such as subject name or date of birth). The unique subject number will be used to label case report form (CRF) data for the subject throughout his/her participation in the study.

The unique subject number for test-arm subjects will begin with the site number (for example, 001) and follow with the subject number (for example, 001).

4.7.2 Enrollment of Control-arm Subjects

Following recruitment, a subject shall be considered enrolled (the point of enrollment) once he or she signs and dates the informed consent form (ICF) prior to completing any study-specific imaging.

Once enrolled, the subject will be assigned a unique subject number, which will not contain information that could identify the subject (such as subject name or date of birth). The unique subject number will be used to label case report form (CRF) data for the subject throughout her participation in the study.

The unique subject number for control-arm subjects will begin with the site number (for example, 001) and follow with a three-digit subject number starting with 3 (for example, 301).

4.8 Criteria for Withdrawal/Discontinuation

A subject may withdraw from study participation at any time, for any reason. The PI may withdraw a subject at any time, for any reason. The reasons for withdrawal and discontinuation for any subject shall be recorded. These will be reported to the Sponsor. The IRB should be notified per their notification of subject withdrawal policy.

A subject shall be withdrawn from the study if diagnostic and/or treatment truth are not known and available. A subject shall also be withdrawn from the study if study-related DTS imaging has not been

completed (i.e. no image is acquired). Information about subject completion is further detailed in Section 4.2 - Number of Subjects.

Data from subjects who may not complete follow-up visits will still be included in analysis, as follow-up is not required as site standard of care. These subjects will not be withdrawn; however, this will be marked on the Case Report Form (CRF).

If a subject withdraws or is withdrawn from the study, all efforts will be made to complete and report study data up to the time of withdrawal. Information about the subject's withdrawal shall be completed and recorded on a CRF. If the reason for withdrawal is related to an adverse event (AE) or serious adverse event (SAE), monitoring of the subject will continue until the outcome is evident.

Any data collected for the subject, up until the time of withdrawal or discontinuation, may still be included in the study results and provided to the Sponsor, unless the subject requests that their data not be used. The site(s) shall document all requests by subjects regarding their data use.

5. STUDY PROCEDURES

5.1 Subject Preparation

Study staff will confirm that subjects are eligible and willing to comply with applicable site requirements prior to starting study procedures. Demographic information, clinical history data, and pregnancy/menopausal status may be collected prior to the study-related imaging procedures.

5.2 Description of Study Procedures

Site technologists will perform image acquisitions and study-related procedures.

5.2.1 Control-arm Subjects

Following subject enrollment and consent, subjects will undergo study-related X-ray imaging and DTS imaging. Imaging results will be collected and recorded. The de-identified radiologist reports will also be collected via scanned copy or DICOM with the associated image sets for each subject. Figure 1 details the study procedures for control-arm subjects.

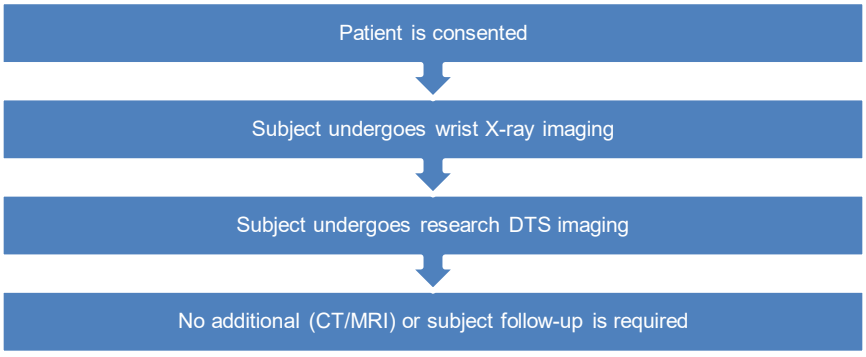

Figure 1. Study Procedures for Control-arm Subjects

5.2.2 Test-arm Subjects

Eligible subjects shall consist of patients presenting with a wrist injury. The patients shall undergo initial X-ray imaging per standard of care (SOC) at the site. If the initial X-ray imaging shows a suspected or

confirmed distal radius or scaphoid wrist fracture, additional imaging, including DTS and/or CT and/or MRI, shall be ordered.

The patient may undergo DTS imaging per site SOC. The subject shall then undergo CT or MRI imaging. The point of enrollment in the study will be the completion of informed consent prior to or immediately after the completion of the SOC CT or MRI exam. The SOC X-ray and/or DTS imaging data shall be collected retroactively from these subjects.

After SOC imaging has been completed, study-specific DTS shall be completed for subjects who have not previously completed SOC DTS imaging.

Subjects shall receive treatment as needed. Diagnostic truth and treatment truth will be collected and recorded on a per-subject basis. The de-identified radiologist and surgical reports will also be collected via scanned copy or DICOM with the associated image sets for each subject. Figure 2 details the study procedures for test-arm subjects.

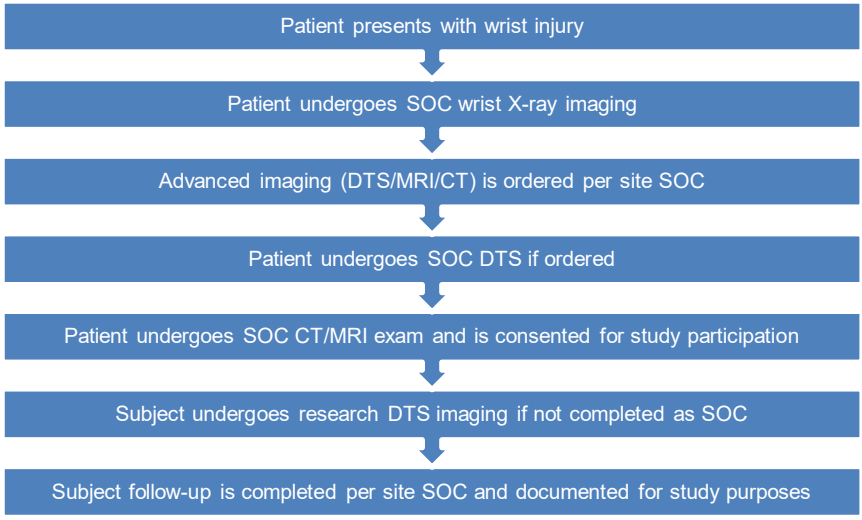

Figure 2. Study Procedures for Test-arm Subjects

5.3 Follow-up

Follow-up may be conducted in this study. Follow-up shall be conducted on a per-subject basis per site standard of care in order to confirm the treatment outcome. Control-arm subjects will not be asked to follow-up.

Subjects will be followed for AEs from the time they enter the imaging suite for their exam(s) until the time they exit the imaging suite after the exam(s).

6. STUDY DATA COLLECTION AND ASSESSMENTS

6.1 Primary Assessment

The device operator will save the images (DICOM and raw data) for all imaging modalities after the subject completes the imaging exams.

Study data will be documented on case report forms (CRFs) as follows:

1) Date of enrollment
2) Demographic information, including age, sex, weight, height, ethnicity, and race

3) Date of image acquisition for:
    a) XR
    b) DTS
    c) CT/MR

6.2 Secondary Assessments

The de-identified radiologist reports will be collected via scanned copy or DICOM with the associated image sets for each subject.

The diagnosis and treatment information on a per-subject basis will be recorded in the study CRF. The following data will be collected:

I. XR Diagnosis
- a. Result of X-ray (Positive, Negative, or Inconclusive)
- b. Left or Right wrist
- c. Type of fracture (scaphoid, distal radius)
- d. Any other fractures in the image field of view– specify

II. DTS Diagnosis
- a. Result of DTS (Positive, Negative, or Inconclusive)
- b. Left or Right wrist
- c. Type of fracture (scaphoid, distal radius)
- d. Any other fractures in the image field of view – specify

III. MRI or CT Diagnosis
- a. Result of CT or MRI (Positive, Negative, or Inconclusive)
- b. Left or Right wrist
- c. Type of fracture (scaphoid, distal radius
- d. Any other fractures in the image field of view – specify

IV. Actual Treatment
- a. No treatment necessary
- b. Non-operative (e.g. splint, cast)
- c. Operative – select all that apply:
    - i. Percutaneous Fixation
    - ii. Open Reduction Internal Fixation (ORIF) (Volar)
    - iii. ORIF (Dorsal)
    - iv. ORIF (Volar and Dorsal)
    - v. External Fixation/Spanning Plate

V. Follow-up
- a. Was follow-up completed for the subject? (Yes or No)
- b. If Yes, was there a change in the treatment? (Yes or No)
- c. If Yes, record the change in treatment

6.3 Safety Assessments

The description, severity, and device relatedness of any AE or SAE during the study will be recorded. Subjects will, if necessary, be provided with emergency care. In the event of any device issues, the event will be recorded. Safety reporting will be conducted as described in this protocol.

7. QUALIFICATION AND TRAINING PLAN

7.1 Staff Qualifications

All members of the study staff participating in the conduct of the clinical investigation shall be qualified by education, training and/or experience to perform their tasks, and this shall be documented appropriately, as per ISO 14155:2011.

7.2 Training Plan for the Protocol and Research Device/Product

Before starting the study, the study staff will be trained on the clinical investigation requirements set forth in this study protocol, including completion of ICFs, CRFs, and other study documentation. Training will also be provided to ensure appropriate storage and handling of data, and all study staff will be required to be trained on Good Clinical Practice (GCP) guidelines per ISO 14155: 2011.

A record of all formal training will be stored in the Site Regulatory Binder and provided to the Sponsor for inclusion in the Sponsor's CHF. Documentation of training will include:

- Title of Training
- Training objectives
- Training logistics (trainer and training method)
- Documentation of trainees
- Training content (e.g. device operation, protocol review, CRF completion)

Study staff directly operating or maintaining VolumeRAD will be qualified by the site(s) based on X-ray imaging experience.

The PI will be ultimately responsible for execution of this study in accordance with the protocol and for device use in this study by members of the study staff.

8. SAFETY

8.1 Anticipated Adverse Events

X-ray imaging involves ionizing radiation. The amount of radiation from a standard X-ray imaging exam, even with the addition of VolumeRAD (study-related DTS), is small and equal in cancer risk to the total body radiation received naturally from the environment over a period of a few months.

There are no known additional medical risks or side effects of VolumeRAD beyond those of similar conventional clinical procedures on other commercial X-ray imaging devices.

The study staff conducting the research is trained to recognize these reactions, and should it be necessary, other medical care is available at the site.

There is always a chance of unexpected risks. Throughout the study, the Sponsor will evaluate and update safety information in study documents.

8.2 Adverse Event Definitions

Adverse Event (AE): any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects, users or other persons, whether or not related to the investigational medical device [ISO 14155:2011 3.2]. This includes events related to the investigational device or the comparator and to the procedures involved. For users or other persons, this is restricted to events related to the investigational medical device.

Serious Adverse Event (SAE): an adverse event that led to death; led to a serious deterioration in the health of the subject, that either resulted in a life-threatening illness or injury, a permanent impairment of a body structure or a body function, or in-patient or prolonged hospitalization, or medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to body structure or a body function; or led to fetal distress, fetal death or a congenital abnormality or birth defect. Planned hospitalization for a pre-existing condition, or a procedure required by the protocol without serious deterioration in health, is not considered a SAE [ISO 14155:2011 3.37].

Adverse Device Effect (ADE): an adverse event related to the use of an investigational medical device [ISO 14155:2011 3.1]. This includes any adverse events resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation, or any malfunction of the investigational medical device. This includes any event that is a result of a user error or intentional misuse of the investigational device [ISO 14155:2011 3.43].

Serious Adverse Device Effect (SADE): an adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event [ISO 14155:2011 3.36].

Device deficiency: an inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety, or performance, such as malfunctions, use errors, and inadequate labelling [ISO 14155:2011 3.15].

Unanticipated serious adverse device effect (USADE): a serious adverse device effect, which by its nature, incidence, severity, or outcome has not been identified in the current version of the risk analysis report [ISO 14155:2011 3.42]. In the United States, any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the study documents, will be reported in accordance with 21 CFR §812.3 and applicable laws and regulations.

8.3 Documentation of Safety Events

All adverse events (AE), including all serious adverse events (SAE), are required to be collected, investigated, and documented during the study reporting period, as defined in the study procedure set forth in this protocol. Documentation will include:

- Description of Event
- Date of onset and resolution
- Severity (mild, moderate, or severe)
    - *Mild*: Symptom(s) barely noticeable to the subject or does not make the subject uncomfortable. The AE does not influence performance or functioning. Prescription drugs are not ordinarily needed for relief of symptom(s).
    - *Moderate*: Symptom(s) of a sufficient severity to make the subject uncomfortable. Performance of daily activities is influenced. Treatment of symptom(s) may be needed.
    - *Severe*: Symptom(s) of a sufficient severity to cause the subject severe discomfort. Treatment for symptom(s) may be given.
- Serious (yes/no)
- Causal relationship to investigational medical device? (not related, possibly related, or related)
    - *Not related*: The adverse event is reasonably expected to be related to (or caused by) a concurrent illness, effect of another device/drug or other cause, and is unlikely related to the investigational product.
    - *Possibly related*: The adverse event is reasonably expected to be related to the investigational product, and an alternative etiology is equally or less likely compared to the potential relationship to investigational product.

- *Related*: There is a strong relationship to investigational product or recurs on re-challenge, and another etiology is unlikely or there is no other reasonable medical explanation for the event.

- Treatment given and/or action taken (procedure stopped, withdrawn from study, or no action)
- Anticipated (yes/no)

8.4 Reporting of Safety Events and Device Deficiencies/Complaints

The following events are to be reported to the Sponsor within 72 hours of the event occurrence and to the EC per their policy:

- All SAEs and USADEs
- All device issues that could possible lead to an SAE

Additional follow-up information may be requested by the Sponsor. In addition, safety information may be shared with regulatory agencies and other participating sites, as required by applicable law and regulation. If the event resulted in the death of a subject, the event shall also be reported via telephone to the Sponsor within 24 hours of knowledge of the event. SAEs will be reported to the IRB per their policy.

Sponsor contact for SAEs and/or UADEs:

Ron Von Jako, MD PhD

Fax: +1-262-364-2544 (24 hours)

E-mail: SAE@ge.com

8.5 Device Deficiencies/Complaints

Device deficiencies/complaints should be reported to the study Sponsor contact identified on the cover page of this protocol. All device deficiencies/complaints will to be collected, fully investigated, and documented in the source document and appropriate case report form (CRF) during the study reporting period. The PI is responsible for notifying the Sponsor in the event that there is any device issue that could potentially lead to a serious adverse event (SAE).

9. ETHICAL CONDUCT OF THE STUDY

The study will be carried out in accordance with the protocol and with principles enunciated in the current version of the Declaration of Helsinki; the guidelines of Good Clinical Practice (GCP) for medical devices, as set forth by ISO 14155:2011 and ISO 14971:2012; applicable sections of US FDA 21 Code of Federal Regulations (CFR); and applicable regulatory authority's requirements of the US.

The study will be conducted and reported in accordance with applicable policies of the ethics committee (EC) and governing regulatory authorities.

If national or regional EC requirements are less strict than the requirements of GCP, such as ISO 14155:2011 for medical devices, the Sponsor shall apply the requirements of this International Standard to the greatest extent possible, irrespective of any lesser requirements, and shall record such efforts.

9.1 Ethics Committee

The responsible PI at each site will ensure that approval from the Institutional Review Board (IRB) is attained for the clinical study prior to enrolling subjects, and the PI will ensure that documentation of approval is maintained for the duration of the study.

The PI will ensure that the Sponsor is notified of any withdrawal of IRB approval within 5 working days of such occurrence. If approval is terminated or suspended, the Principal Investigator will promptly notify the Sponsor and provide written explanation.

9.2 Regulatory Agencies and Competent Authority(ies)

The Sponsor will obtain approval from the IRB before the start of the clinical trial, if necessary, per applicable local laws and regulations. Any additional requirements imposed by the EC or regulatory authority shall be followed, if applicable.

9.3 Management of Protocol Modifications and Amendments

Substantial amendments will only be implemented after approval of the IRB.

A deviation is any instance(s) of failure to follow, intentionally or unintentionally, the requirements of the protocol. Under emergency circumstances, deviations from the protocol to protect the rights, safety, and wellbeing of human subjects may proceed without prior approval of the Sponsor and the IRB. Such deviations shall be documented and reported to the Sponsor and the IRB as soon as possible. Deviations will be reported as:

- **Critical Deviations:** Deviations that significantly affect the safety, efficacy, integrity, or conduct of the study. These deviations must be reported to the Sponsor no later than 5 working days from awareness of occurrence and reported to the IRB per the deviation reporting policy.
- **Non-Critical Deviations:** Protocol deviations that do not significantly affect the safety, efficacy, integrity, or conduct of the trial. These deviations must be documented on the CRF Protocol Deviation page and will be reviewed by the study monitor.

Non-substantial modifications may be made during the normal course of device optimization, maintenance, and feasibility testing. Non-substantial modifications will be communicated to the IRB as soon as possible.

9.4 Participant Information and Informed Consent

The PI will explain to each participant the nature of the study, its purpose, the procedures involved, the expected duration of exposure to the investigational device (if applicable), the potential risks and benefits, and any potential discomforts. Each participant will be informed that participation in the study is voluntary, that he/she may withdraw from the study at any time, and that withdrawal of consent will not affect his/her subsequent medical assistance and 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 the study will be provided an ICF, describing the study and providing sufficient information to allow the participant to make an informed decision about his/her participation in the study. Informed consent documents will be subject to approval by the IRB prior to enrolling subjects in the study.

The participant should read and consider the statement before signing and dating the ICF, and shall be given a copy of the signed document. The ICF must also be signed and dated by the PI (or his/her designee), and it shall be retained as part of the study records.

9.5 Early Termination of the Study

The Sponsor may terminate the study prematurely according to certain circumstances. Examples of such circumstances include ethical concerns, insufficient participant recruitment, participant safety concerns, alterations in accepted clinical practice that make the continuation of a clinical trial unwise, early evidence of benefit or harm of the research product, or for any other reason.

10. STATISTICAL METHODS

10.1 Statistical Hypothesis

No statistical hypothesis is being tested in this data collection study. The results of this study will be reported in the form of descriptive statistics.

10.2 Sample Size Determination

A target of at least 31 scaphoid and 31 distal radius wrist fractures are required in order to establish a sufficient data set for use in future research and/or clinical validation activities. Additionally, at least 25 healthy subjects are required to compare diagnostic and treatment truth of subjects with a wrist fracture against a healthy subject population. The overall data set will consist of up to 140 subjects in the following categories:

- Up to 50 subjects presenting scaphoid fractures, to achieve a target of at least 31 enrolled subjects
- Up to 50 subjects presenting distal radius fractures, to achieve a target of at least 31 enrolled subjects
- Up to 40 healthy subjects, to achieve a target of at least 25 enrolled healthy subjects

10.3 Statistical Analysis

No statistical analysis is prospectively planned. The study data will be presented in tables, listings, and figures. Data will be summarized using descriptive statistics. The descriptive statistics for continuous variables will include mean, standard deviation, median, Q1 and Q3, minimum, maximum, and sample size, as appropriate. Categorical variables will be described with counts, percentages, and sample size, as appropriate.

10.3.1 Interim Analysis

No interim analyses are intended to be conducted as part of this study.

10.4 Handling of Missing Data

Analysis will be based on collected data, and no imputation will be done for missing data.

10.5 Deviation(s) from the Original Statistical Plan

Any changes or deviations from the original statistical plan specified in this protocol will be described and justified in the study final report per ISO 14155:2011.

11. QUALITY ASSURANCE AND CONTROL

11.1 Data Management

Data management processes for handling study data will be maintained by the Sponsor.

11.1.1 Completion of Case Report Forms (CRFs)

The data reported on the eCRFs shall be derived from source documents and be consistent with these source documents. Electronic CRFs (eCRFs) will be used to collect data. The Sponsor will provide eCRFs and train study staff on completion of eCRFs using Good Documentation Practices (GDP). CRF Completion Guidelines (CCG) may be provided by the Sponsor to help facilitate training.

eCRFs are to be completed as information becomes available at the site. CRFs should be signed by indicated parties, in indicated area(s), to certify the contents of the form. The PI is ultimately responsible for ensuring completion of eCRFs.

In the event that any discrepancies are discovered on the eCRF, whether during monitoring or during data review by the study team, a query will be raised, and the site shall make the correction within the electronic database, noting the reason for change. Data will be considered clean once all queries are answered and closed.

If the Sponsor discovers discrepancies on eCRFs, a query will be raised and necessary corrections will be made by the site. The reason for any changes will be noted. All queries will be resolved prior to study completion.

11.1.2 Data Handling and Record Keeping

All documents and data shall be produced and maintained in a manner that assures control and traceability.

11.1.3 Source Data and Documents

Source data includes information in original records, certified copies of original records of clinical findings, observations, or other activities for the study. Source documents for each subject must be retained throughout the investigation, including printed or electronic documents containing source data. Elements should include:

- **Source data and documentation** relevant to data recorded for subject screening and CRF corroboration
- **Subject records** containing the completed ICFs and CRFs
- **Regulatory binder** containing the protocol and any subsequent amendments, EC submissions and approvals, blank ICF(s), and site logs
- **Reference manuals** containing investigator responsibilities, Sponsor, AE/SAE and informed consent guidelines, applicable study aids and training materials

The PI or institution shall provide direct access to source data during and after the clinical investigation for monitoring, audits, EC review, and regulatory authority inspections.

11.1.4 Archiving

All study data must be archived for a minimum of four (4) years after study termination or premature termination of the clinical trial. No source documents or study records will be destroyed without Sponsor notification and approval.

12. MONITORING PLAN

In collaboration with the site, the Sponsor will ensure proper monitoring of the study to confirm that all the research requirements are met. Monitoring visits will oversee the progress of a clinical investigation and ensure that it is conducted, recorded, and reported in accordance with the protocol, written procedures, Good Clinical Practice (GCP) ISO 14155:2011, and the applicable regulatory requirements.

12.1 Confidentiality and Data Protection

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

Individual subject medical information obtained as a result of this study will be considered confidential, and disclosure to third parties will be prohibited. Subject confidentiality will be further ensured by utilizing subject identification code numbers. For data verification purposes, authorized representatives of the Sponsor or IRB may require direct access to parts of the medical records relevant to the study, including subject medical history.

12.1.1 Storage of Images and Associated Health Data

Images and associated data will be collected and disclosed to the Sponsor as part of this study. Fully de-identified data, which has had all personal identifying information removed, may be stored and used by the Sponsor indefinitely. The Sponsor and/or its authorized representatives may use any de-identified data collected in this study for future technology and engineering development, marketing purposes, education, regulatory submissions, publications, or other possible uses.

12.2 Publication Policy

The results of this study may be used in future publications. The conditions of publication are described in a separate contractual agreement.

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7. 510(k) Summary Premarket Notification Submission. FDA.gov. https://www.accessdata.fda.gov/cdrh_docs/pdf13/K132261.pdf. Published July 18, 2013.

8. Center for Devices and Radiological Health. Medical X-ray Imaging. U S Food and Drug Administration Home Page. https://www.fda.gov/Radiation-EmittingProducts/RadiationEmittingProductsandProcedures/MedicalImaging/MedicalX-Rays/default.htm.

APPENDIX A – STUDY SITE AND INVESTIGATOR LIST

The following investigators at each study site will be responsible for the conduct of this study:

Investigator(s):[1]	**David R. Steinberg, MD** *Tel*: +1-856-220-6985 *e-mail*: David.Steinberg@uphs.upenn.edu	**University of Pennsylvania Hospital – Department of Orthopaedic Surgery (Site 001)** *Address*: 3737 Market Street, Penn Medicine University City Philadelphia, PA 19104 US
	Investigator Name TBD *Tel*: TBD *e-mail*: TBD	**Site Name (Site 002)** *Address*:

[1] The role of the ***Principal Investigator*** is to implement and manage the conduct of the investigation as well as ensure data integrity and the rights, safety, and well-being of humans involved in the study [ISO 14155:2011 9.1]. ***Co-Investigators*** share all responsibilities of the ***Principal Investigator***, and ***Sub-investigators*** share only those responsibilities designated by the ***Principal Investigator***.

APPENDIX B – AMENDMENTS (PROTOCOL VERSION 1.0 TO 2.0)

A detailed amendment is provided for Version 1.0 to Version 2.0. Version 1.0 received EC approval but was not active at the site.

Purpose of Amendment: This amendment was generated to update the Sponsor contact information as well as device risk and safety information. These changes are not expected to impact operator risk or to adversely impact the scientific integrity or conduct of the study. Administrative changes that improve grammatical clarity and formatting changes were not recorded.

In the table below, point-by-point revisions are shown as additions in double-underline (double-underline) and deletions in strikethrough (~~strikethrough~~) for each change made in this amendment from the previous version.

Item	Section	Revision or Clarification	Justification
1	8.1 Anticipated Adverse Events	X-ray imaging involves ionizing radiation. The amount of radiation from a standard X-ray imaging exam, even with the addition of VolumeRAD (study-related DTS), is small and equal in cancer risk to the total body radiation received naturally from the environment over a period of a few months. There are no known additional medical risks or side effects of VolumeRAD beyond those of similar conventional clinical procedures on other commercial X-ray imaging devices. ~~Foreseeable AEs that apply to X-ray imaging and are also applicable to imaging using VolumeRAD may include, but are not limited to:~~ • ~~Skin reddening or irritation that may occur due to long periods of exposure to relatively high levels of radiation (rare for many types of imaging exams)~~ The study staff conducting the research is trained to recognize these reactions, and should it be necessary, other medical care is available at the site. There is always a chance of unexpected risks. Throughout the study, the Sponsor will evaluate and update safety information in study documents.	Updated to provide clarity per recommendation from EC review.
2	Administrative Structure of Investigation	Clinical Affairs Project Manager **(Sponsor Contact)**:	**~~Stephanie Karwedsky~~ Beth Heckel** *Tel:* +1-262-~~443-7008~~312-7269 *e-mail*: ~~Stephanie.Karwedsky@ge.com~~ Beth.Heckel@med.ge.com	**GE Healthcare (GEHC)** *Address*: 3000 N Grandview Blvd Waukesha, WI 53188 US	Updated to reflect change in Sponsor contact information.