[redacted]

GE Healthcare

Clinical Study Protocol:

Automated Breast Ultrasound Case Collection Registry

(STUDY NO. 110.01-2016-GES-0001)

Version: 3.0; 09/Jan/2018

[redacted]

Device/Product: GE Invenia Automated Breast Ultrasound System (ABUS)

Modality: Ultrasound (U/S)

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.

[redacted]

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The Sponsor and 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 investigator 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

[redacted]

Table of Contents

[redacted]

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	Revision Author	Comments/Changes
1.0	14/Feb/2016	[redacted]	Clinical Writer – This is the initial version.
2.0	27/Oct/2017	[redacted]	Clinical Writing Specialist – Amended for updates to Sponsor Contact, Medical Monitor, Device/Product information, and clarification and correction of minor errors throughout document.
3.0	09/Jan/2018	[redacted]	Clinical Writing Specialist—Clarify follow up and general data collection.

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LIST OF ABBREVIATIONS AND TERMS

2DS	2D Synthetic Digital breast tomosynthesis
ABUS	Automated breast ultrasound
ACS	American Cancer Society
ADE	Adverse Device Effect
AE	Adverse Event
ALARP	As Low as Reasonably Possible
AMA	American Medical Association
CA	Competent Authority
CAD	Computer-aided detection
CAPM	GE Clinical Affairs Project Manager
CCG	Case Report Form Completion Guidelines
CESM	Contrast enhanced spectral mammography
CFR	Code of Federal Regulations
[redacted]	[redacted]
CRF	Case Report Form
DBT	Digital breast tomosynthesis
DCF	Data Clarification Form
EC	Ethics Committee
EU	European Union
FDA	United States Food and Drug Administration
FFDM	Full-field digital mammography
GCP	Good Clinical Practice (see ISO 14155:2011) [1]
GE	General Electric
GEHC	General Electric Healthcare
HHUS	Hand-held ultrasound
ICF	Informed Consent Form
ISO	International Standards Organization
MRI	Magnetic resonance imaging
[redacted]	[redacted]
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

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STUDY SYNOPSIS

Sponsor:	General Electric Company, acting through its GE Healthcare Business
Research Type:	This is a prospective multi-site study of the GE automated breast ultrasound (ABUS) system and other breast imaging modalities already used in clinical practice. The study aims to create a registry of breast exam patients. No blinding, therapeutic interventions, or masking are employed.
Regulatory Status:	This is study is a study of post-market devices used on and off label (in accordance with standard clinical practice at the site), including the following commercially available devices: • GE Invenia Automated Breast Ultrasound System (ABUS) and • Digital Breast Tomosynthesis (DBT) All devices used in the study are considered post-market and are used in accordance with their labeling, [redacted] The study may also use accessory devices and commercial image workstations to view and interpret images. In the US, DBT and ABUS are class III medical devices. Research activities will be subject to applicable sections of 21 CFR 812.2(b)(1).
Background and Rationale:	[redacted] This prospective study aims to collect longitudinal data in women with dense breasts undergoing ABUS as a supplement to digital breast tomosynthesis (DBT). [redacted]
Procedures/ Methods:	Data will be collected from eligible women who have been prescribed or have completed DBT and ABUS, screening within a 30-day window. Radiologist evaluations and, when performed, outcomes of biopsy and/or laboratory testing will be recorded. Subjects will be followed for breast cancer status and results of any diagnostic breast exams and/or treatment.
Objectives:	*Primary*: To establish a longitudinal registry of breast imaging datasets from GE ABUS and other technologies (DBT, and, when performed, other screening & diagnostic breast exams or testing) that will facilitate future breast cancer care pathway research.
Endpoints:	*Performance*: The type of exams performed per patient (ABUS, DBT and, if applicable, other exams, such as FFDM, HHUS, 2D Synthetic (2DS), or MRI) *Efficacy*: Breast cancer (cancer/non-cancer) status following initial diagnostic exams and at follow-up (breast cancer status and, if applicable, breast diagnosis and treatments). *Safety*: Safety will be assessed by AE and SAE occurrence.

Eligibility criteria:	**Inclusion criteria:** Subjects who meet all the following inclusion criteria may be included: 1. Are asymptomatic adult women (aged 18 years or older); 2. Are eligible to complete or have completed (within 30 days) screening ABUS and DBT exams per the site standard of care;[1] 3. Have heterogeneously dense and extremely dense breasts (BI-RADS C or D, respectively) or are determined to have dense breasts prior to the study on initial screening mammography; 4. Are able and willing to participate.	**Exclusion criteria:** Subjects who meet any of the following exclusion criteria will not be included that: 1. Have a breast cancer diagnosis (with or without metastasis) or are being treated for breast cancer within the year prior to the study.
Sample size and Sites:	Up to 10,000 (ten thousand) women may participate in the registry at up to 10 participating sites. [redacted] Per-site enrollment will be based on actual throughput of qualifying patients.	
Study duration:	The study is expected to last approximately 6 years, which includes approximately 5 years of enrollment and additional follow-up of the last patient in.	

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[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

1. BACKGROUND AND JUSTIFICATION

This study is being conducted to collect longitudinal data from breast cancer screening of patients who receive ABUS exams along with DBT, and sometimes other technologies. The study aims to collect information about cancer detection, treatment, and outcomes based on individual and combined assessment technologies.

2. DEVICE DESCRIPTION

This is a prospective post-market study of commercially available GE ABUS used along with and primary screening modalities such as DBT & FFDM, and other supplemental screening modalities such as MRI and HHUS.

2.1 Identity, Mechanism, and Function

2.1.1 GE Invenia (Generation II) Automated Breast Ultrasound ~~System (ABUS)~~

Name: GE Invenia (Generation II) Automated Breast Ultrasound ~~System (ABUS)~~

Modality/Type: Ultrasound (U/S)

Manufacturer: GE

Software version: Current commercially available software version

Regulatory Status: Post-market

Note: No devices will be issued by the Sponsor exclusively for study use. Unique identifying information for devices used at the site will be recorded as part of the device accountability record for the study.

[redacted]

2.1.2 Standard of Care Breast Imaging Devices and Accessories

Full-field digital mammography (FFDM) devices are either integrated systems that include both the X-ray delivery system and integrated (non-removable) detector, or detector-only (removable) systems intended to be used on existing X-ray systems where the removable detector, such as a computed radiography cassette replaces the film/screen detector. These systems are widely commercialized and regularly used in breast cancer screening.

Digital Breast Tomosynthesis (DBT) systems are designed to collect 3-dimensional x-ray images of breast tissues. DBT enables acquisition using partial isocentric motion (detector stationary and X-ray tube moving in an arc based on the pivot point designed to be used for stereotactic imaging). DBT also enables capture of 2D synthetically reconstructed views that are similar to FFDM images.

Other site-provided commercial devices may be used per the local site standard of care, such as MRI, CESM, automated US from other vendors, and HHUS exams. Images may be viewed on standard commercially available imaging workstations at the site in accordance with standard practices.

2.1.3 Use of Devices in Research per the Standard of Care

This study involves the use of post-market (commercially available) devices utilized according to the site standard of care. [redacted] Collection of research data from imaging scans will be conducted in accordance with applicable laws and regulations of the United States, including applicable sections of US FDA 21 CFR.

[redacted]

2.2 Intended Use

The GE Invenia Automated Breast Ultrasound System (ABUS) is intended to be used for as an adjunct to mammography or breast cancer screening in asymptomatic women for whom screening mammography findings are negative or benign (BI-RADS 1 or 2), with dense breast parenchyma, and have not had previous clinical breast intervention. All procedures will be used as per the site standard of care. This study involves use of ABUS devices in the representative

clinical population, [redacted] Participating in the study poses minimal risk to subjects as devices are used as they would be in the standard of care were the subject not participating in the registry study.

2.3 Concomitant/Ancillary Administrations

No medication administrations (such as contrast or sedatives) will be given or withheld for this study.

2.4 Accountability

Accurate and adequate records will be maintained for all devices used in the study, including recording the unique identifying information for systems used on the study (which may include serial numbers, make, model, and information about the hardware and software used). The Principal Investigator will be ultimately responsible for the security and integrity of devices used in this study.

2.4.1 Issuance

All study devices will be provided and maintained by the participating sites. This may include devices that are under contract from the Sponsor, when under site control.

2.4.2 Disposition

Study devices are post-market and used in accordance with site operating procedures. Any data specific to research (such as subject identification numbers or other study-specific information) will be removed after the study ends.

2.5 Anticipated Risks and Benefits

The GE ABUS device and the other breast cancer detection devices and treatments studied in this trial are post-market and will be used according to the standard of care at the investigational sites. The safety profile of ABUS and DBT are well understood and already used as part of the standard of care at many sites. Thus, risk from participating in this study is minimal for all patients.

In the rare case that medically important incidental findings are observed in the study that would not otherwise have been observed as part of regular medical care, the study doctor may communicate these findings to the subject and medical management may be necessary outside of the study. [redacted] The research does not have other direct benefits, but may benefit future patients by improving understanding of the role of ABUS in breast care.

As part of this study, some subjects may have an additional exam (ABUS or DBT) that they would not otherwise have had as part of their clinical care, but the total cumulative exposure is expected to be well within normal clinical ranges for breast exams. As with any research study, there is a risk of loss of confidentiality. Because the registry uses no identifiable information, this

risk is considered minimal. Exposure to ionizing radiation during DBT exams is minimal and well below doses widely accepted as safe. FFDM and DBT will only be used concurrently at sites where that is considered standard of care breast screening. ABUS involves use of acoustic energy and does not expose the patient to additional ionizing radiation. Study exams do not pose exposure risks beyond those typically encountered during clinical breast cancer screening.

As for any research study involving creation of a registry bank for data, there is a risk of loss of confidentiality. To protect subjects, no identifiable information will be stored in the registry, and the site and sponsor will ensure that data containing identifiable information are secure and that the risk of loss of confidentiality is as low as reasonably possible (ALARP) throughout the study. Subjects may be contacted to schedule follow-up visits, and reasonable controls will be placed to ensure that subject contact information remains confidential.

2.5.1 Risk Category and Rationale

According to US regulation, the use of the investigational GE Invenia Automated Breast Ultrasound System (ABUS) in this study designates it as a non-significant risk device per the 21 CFR 812.3 (m) Definitions, under the following rationale:

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

The GE Invenia ABUS system and DBT systems are Class III medical devices in the United States.

3. STUDY OBJECTIVES AND ENDPOINTS

3.1 Purpose of the Study

The contribution of automated breast ultrasound (ABUS) to the screening pathway for breast cancer is not fully understood. This prospective study aims to collect longitudinal data in women with dense breasts undergoing ABUS as a supplement to primary screening methods, such as digital breast tomosynthesis (DBT) and as full-field digital mammography (FFDM). [redacted]

3.1.1 Primary Objective:

To establish a longitudinal registry of breast imaging datasets from GE ABUS and other technologies (DBT, and, when performed, other screening & diagnostic breast exams or testing) that will facilitate future breast cancer care pathway research.

3.2 Study Endpoints

3.2.1 Performance Endpoints

The type of exams performed per patient (ABUS, DBT, and, if applicable, other exams, such as FFDM, HHUS, 2D Synthetic (2DS), or MRI)

3.2.2 Efficacy Endpoints

Breast cancer (cancer/non-cancer) status following initial diagnostic exams and at follow-up (breast cancer status and, if applicable, breast diagnosis and treatments; see 5.2.4. Follow-up).

3.2.3 Safety Endpoints

Type and number of AEs, SAEs, and device issues will be recorded. Adverse events and devices issues not reflected on the product label will be reported to the manufacturer and, for GE products, will be dispositioned according to the Sponsor's complaint handling procedures for post-market products.

3.3 Summary of Study Design

This is a prospective multi-site study of the GE automated breast ultrasound (ABUS) system and comparable modalities already used in clinical practice. The study aims to create a registry of breast exam patients. No blinding, therapeutic interventions, or masking are employed.

4. STUDY DESIGN

4.1 Study Population

This study will enroll adult women with dense breasts clinically referred for breast cancer screening. As this study is expected to span multiple years, during which time these recommendations may be revised or updated, the most current applicable guidelines for mammographic screening should be employed in this study, at the discretion of the site.

4.2 Number of Subjects

Up to 10,000 women may participate in the registry at up to 10 participating sites. Enrollment is based on a minimum population estimated to be necessary to draw population-based inferences in future analysis. Per-site enrollment will be based on actual throughput of qualifying patients. The study is expected to last approximately 6 years, which includes approximately 5 years of enrollment and approximately 1 additional year to complete follow-up of the last patient in.

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.

This study does not target any groups of subjects considered to be vulnerable subjects in the United States. However, as the study is expected to pose minimal risks to subjects, vulnerable

subjects that incidentally present at the site and qualify for participation (such as pregnant women, employees or faculty of the site, and students) will not be prohibited from participating in the registry where acceptable per governing IRB policy. No participants will be under undue influence to participate.

The Sponsor and all investigators 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.

4.4 Eligibility Criteria

4.4.1 Inclusion Criteria

Subjects who meet all the following inclusion criteria may be included:

1. Are asymptomatic adult women (aged 18 years or older);
2. Are eligible to complete or have completed screening ABUS, DBT, as determined by the site;
3. Have heterogeneously dense and extremely dense breasts (BI-RADS C or D, respectively), or are determined to have dense breasts prior to the study on initial screening mammography;
4. Are able and willing to participate.

4.4.2 Exclusion Criteria

Subjects who meet any of the following exclusion criteria will not be included that:

1. Have a breast cancer diagnosis (with or without metastasis) or are being treated for breast cancer within the year prior to the study.

4.5 Recruiting and Screening

Subjects will be identified for inclusion in this registry study according to the standard procedures of the investigational site and in accordance with governing IRB policy. Participation in this study is voluntary and will not impact how the subject's clinical exams are performed. Subjects may be included in the registry that are part of any of the following subpopulations studied:

1. **ABUS/DBT Cohort** – Subjects enrolled to the study where no imaging exams are required in the study period, as all required imaging exams, ABUS, and DBT, were completed within 30 days of enrolling in the study.
2. **ABUS-only Cohort** – Subjects recruited to the study that have already completed DBT before enrolling in the study and will undergo an ABUS exam during the study period. All exams should be completed in a 30-day window.
3. **DBT-only Cohort** – Subjects recruited to the study that have already completed ABUS before enrolling in the study and will undergo a DBT exam during the study period. All exams should be completed in a 30-day window.

Following recruitment, a subject will be considered enrolled (the point of enrollment) once he/she signs and dates the informed consent form (ICF), except in cases where consent is waived in accordance with IRB determination (in which case enrollment is considered to start when the subject's information is recorded and monitored by the Sponsor). 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 study data throughout the study.

4.6 Criteria for Withdrawal/Discontinuation

A subject may withdraw from study participation and/or request that her data not be included in the registry at any time, for any reason. The investigator 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 EC should be notified per their notification of subject withdrawal policy. Any data and images collected for the subject up until the time of withdrawal or discontinuation, may still be included in the study registry and provided to the Sponsor, unless the subject requests that their data not be used. The site shall document all requests by subjects regarding their data use.

5. STUDY PROCEDURES

5.1 Subject Preparation

No preparation beyond that required by the site standard of care is required.

5.2 Description of Study Procedures

5.2.1 Patient Procedures

Data will be collected from exams performed on eligible women that have completed or will complete (within a 30 day window) DBT and ABUS exams for breast screening. If a subject has completed one or more of these exams, but not both, she will be asked to have the remaining exam(s) as during the study period.

If a subject has already been prescribed exam(s) for her regular medical care, the exam will be performed as prescribed. All exams are performed on post-market devices according to the site standard of care at the site and may be used for medical management.

The study does not require any therapeutic intervention or change in medical care.

5.2.2 Site Image Reads

A clinician reader at the site will review DBT ABUS, and any additional imaging completed and the reader's findings will be reported on a case report form (CRF) provided by the Sponsor and stored in the study registry. If a biopsy was performed and resulted in negative or benign cytology or histopathology, the reader will review the subject's imaging and histopathology findings for concordance. If the imaging and histopathology findings are discordant, re-biopsy and resulting histopathology may be required per the site's standard of care.

5.2.3 Breast Cancer Status

The site determined breast cancer status (cancer/non-cancer) for each subject based on all available clinical information will be collected. Results of any additional exams prescribed for the subject's regular medical care for breast cancer, including biopsy, MRI, HHUS, other imaging exams, and/or laboratory tests may be recorded and disclosed to the Sponsor and used in the study registry.

5.2.4 Follow-up

No in-office follow-up is required, except as necessary for the patient's regular medical care. Medical records and subject contact (emails/phone calls) may be used to confirm follow-up results, or subjects may be contacted to follow-up during their regular clinical visits. To help increase follow up responses from patients and decrease dropout from the study, the following are options for follow up that can occur 12 months to 30 months after ABUS scanning for this study (for non-cancer patients)

- Mammogram (FFDM or DBT)
- MRI
- Ultrasound (ABUS or HHUS)
- Histology (surgery and/or biopsy)
- If follow up imaging is unable to be collected within 18 months, clinical state assessment via chart review and/or follow up contact with the subject at 18 to 30 months.

Positive cancer subject's follow-up will be completed within 12-18 months after ABUS scanning for this study. Follow-up may be done by chart review and/or follow up contact with the subject.

6. STUDY DATA COLLECTION AND ASSESSMENTS

6.1 Data Collection for Subject Information and Breast Exams

A subject case report form (Subject CRF) will be provided by the Sponsor that includes the following:

- Subject ID and demographics (including age, gender, ethnicity, and race)
- Relevant medical history (at minimum pregnancy history, history of breast surgeries and interventions, history of breast cancer, history of hormone therapy, breast implants, radiation therapy involving chest wall, known gene mutations.)
- DBT Exam Information (i.e. dates, breast density score, findings, etc.)

  Note: To be included in the registry, an ABUS exam must be performed on a GE device. When other automated and/or conventional ultrasound images are obtained incidentally outside of this study, those images and the make and model of the acquisition device may be collected and disclosed as part of study data. Data may be collected electronically, based on agreement between the Sponsor and investigator.
- ABUS exam information (i.e. dates, views, findings, etc.)
- Additional exam information (FFDM, HHUS, 2D Synthetic (2DS), CESM, and/or MRI)

- Histology information (i.e. procedures, results, etc.)

6.2 Data Collection for Follow-up

A follow-up case report form (Follow-up CRF) will be provided by the Sponsor. For subjects diagnosed with breast cancer prior to follow-up, this could include treatment/outcomes and follow up dates. For subjects diagnosed non-cancer prior to follow-up, this could include type(s) of follow-up (mammography, MRI, ultrasound, histology w/ concordance, chart review, and/or subject contact), information on any imaging, information on histology, etc.

6.3 Image Data Collection

The image data from the ABUS and DBT exams completed within 30 days of each other and within 30 days of enrollment will be collected after the subject enrolls in the research study.

If applicable and available, other exams, such as additional ABUS and DBT, FFDM, HHUS, 2D Synthetic (2DS), CESM, or MRI exams completed up to 30 days prior to enrollment until subject completion of study will be collected after the subject enrolls in the research study.

Sites will use a standard anonymization process to de-identify all image data collected for this study.

6.4 Safety Assessments

The description, severity, and device relatedness of any AE or SAE occurring during the study will be recorded. AE/SAEs will be recorded that occur during the study period, whether the exam is prescribed outside of the study or performed as part of the study (after the subject is enrolled). Data and images may be collected observationally from ABUS and DBT or other imaging exams performed prior to the date that a subject enrolls in the study (within a 30-day window), but safety events occurring before the enrollment in the study may not be tracked (this data may, however, be collected to supplement the registry data, when available). 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 Study Staff and Reader Qualifications

All members of the study staff participating in the conduct of the investigation shall be qualified by education, training, and/or experience to perform their tasks, and this shall be documented appropriately, as per applicable regulatory requirements for the conduct of observational trials.

All image readers will be qualified to practice according the local requirements of the site. The Sponsor may request copies of the medical license, curriculum vitae, years in practice, and other information about the study readers to confirm qualification to assess images.

7.2 Training Plan for the Protocol

Before starting the study, the study staff will be trained on the clinical investigation requirements set forth in this study protocol according, including:

- Training for the protocol and registry
- Training objectives, which may include collecting and confirming data, reading images, and assisting in monitoring and conduct of the trial
- Training logistics, which may be performed by a qualified employee or consultant of the Sponsor
- Target audience, based on study role
- Training content, such as review of the protocol and consent procedures and registry data handling

The Sponsor will not provide training or otherwise intervene in normal use of the study devices at participating sites, which will follow their site standard of care in acquiring and evaluating images, including the use of FDA approved CAD. Study staff directly operating or maintaining the research device or product will be qualified based on experience by the participating sites.

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

8. SAFETY

8.1 Anticipated Adverse Events

This study involves only the use of post-market devices used in accordance with the site standard clinical care, and is not expected to pose additional medical risks to subjects beyond those of a routine clinical exam of similar type.

8.1.1 GE Invenia ABUS

The Invenia ABUS system is not known to have risks beyond those of routine ultrasound, which involves minimal risk because it does not utilize x-rays or other ionizing radiation. The risks of ultrasound include:

- Tissue warming
- Discomfort
- Skin irritation
- Bruising
- Abrasions or tears in the skin

In rare cases, formation of small pockets of gas in body fluids or tissues (cavitation) can occur. The long-term effects of cavitation are unknown. These risks are not changed or increased by participating in this study.

8.1.2 Full-field Digital Mammography and Digital Breast Tomosynthesis Risks

FFDM involves exposure to low-dose x-ray radiation, but the benefits are considered to outweigh the risks for subjects prescribed this care for breast cancer screening. Excessive exposure to ionizing radiation in x-ray exams can, in rare cases, cause cataracts, skin

reddening, and hair loss. There are no known additional risks or side-effects specific to tomosynthesis aside from the radiation risk associated with all imaging tests involving ionizing radiation. Risks associated with FFDM and DBT exams include:

- Discomfort
- Skin irritation
- Bruising
- Abrasions or tears in the skin

Participating in this study does not change the type or dose of x-ray radiation any subject will receive. Thus, the chance of these risks occurring will not be changed or increased by participating in this study.

8.1.3 Reporting Unexpected Risks

Because this study spans a multi-year period, it is expected that many subjects will have unrelated medical care during the study period. All adverse events that occur while the subject is having ABUS, DBT exams under study should be reported, whether or not related to the study devices. Adverse events that may be related to study exams or devices should be reported throughout the study period. It is not required to report incidental illness or medical events between follow-up visits that are not considered related to breast health.

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 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.

8.5 Device Complaints

This is a post-market study of commercially available devices that are manufactured by GE and other manufactures. Issues with post-market devices should be reported to the manufacturer of the device. For device issues reported for the GE ABUS device or other GE devices observed in the study, issues should be reported to the Sponsor and will be handled according to the Sponsor's procedures for handling post-market complaints regarding commercial products. Device complaints should be reported to the study Sponsor contact identified on the cover page of this protocol.

All device complaints should be collected, fully investigated, and documented in the source document. The Principal Investigator is responsible for notifying the Sponsor in the event that there is any device issue that could potentially lead to a SAE or otherwise pose a safety risk to subjects or operators.

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 14971:2010; applicable sections of US FDA 21 CFR; and applicable regulatory authority's requirements in the United States.

The study will be conducted and reported in accordance with applicable policies of the site's governing Ethics Committee (EC) and governing regulatory authorities.

9.1 Ethics Committee

The responsible Principal Investigator at each site will ensure that approval from an appropriately constituted EC is attained for the clinical study prior to enrolling subjects, and Principal Investigator will ensure that documentation of approval is maintained for the duration of the study.

The Principal Investigator will ensure that the Sponsor is notified of any withdrawal of EC 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)

No prospective regulatory approval is required for post-market studies conducted in the United States. Any additional requirements imposed by the EC or regulatory authority shall be followed, where applicable.

9.3 Management of Protocol Modifications and Amendments

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

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 EC/competent authority (CA). Such deviations shall be documented and reported to the Sponsor and the EC 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 EC 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 CA as soon as possible, if applicable, and to the EC per their policy.

9.4 Participant Information and Informed Consent

Where required by the governing IRB, evidence of written informed consent will be attained. During the process of consenting, the investigators will explain to each participant the nature of the study, its purpose, the procedures involved, the expected duration of exposure to the investigational device, the potential risks and benefits, and any potential discomforts. Consent will include informing the patient that participation in the study is voluntary, that she may withdraw from the study at any time, that withdrawal of consent will not affect her subsequent medical assistance and treatment, and that her medical records may be examined by authorized individuals other than her treating physician. The informed consent form will describe the study and providing sufficient information to allow the participant to make an informed decision about her participation in the study.

Informed consent documents will be subject to approval by the IRB prior to enrolling subjects in the study. Informed consent may not be required for some populations under study, at the discretion of the governing IRB at each participating site. In the event that any population/site qualifies for waiver of consenting requirements in accordance with local IRB requirements, a copy of the IRB determination will be stored in site regulatory binders and in the Sponsor's Clinical History File (CHF).

Where evidence of written informed consent is required by the governing IRB, the participant shall be provided time to read and consider study information and will then sign and date the

ICF, and shall be given a copy of the signed document. The ICF must also be signed and dated by the investigator (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 study.

10.2 Sample Size Determination

The sample size of 10,000 subjects is based on estimations of actual accrual possible within the allotted study period at participating sites. Breast cancer registries have been conducted that include from several hundred to multiple thousands of subjects. [3, 5, 14] The sample size of this study is estimated based on the populations at the investigational site and the Sponsor's engineering estimations in order to provide a representative sample of the clinical population

10.3 Statistical Analysis

No statistical analysis is prospectively planned. The number of exams by type and per patient cancer status, outcomes, and treatment may be summarized using descriptive statistics. Disposition of all enrolled subjects and occurrence of AE/SAEs and devices issues will be summarized in the final report for the study.

10.3.1 General Statistical Methods

Study data may 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. Categorical variables will be described with counts, percentages, and sample size. A 95% confidence interval may be presented, when necessary. Additional *ad hoc* analyses, if necessary, will be documented prior to execution.

10.4 Handling of Missing Data

In the event of missing data, sites may be asked to clarify or provide additional information. No additional imputation for missing data is planned.

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

CRFs 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 Principal Investigator is ultimately responsible for ensuring completion of CRFs.

If discrepancies are discovered on CRFs during monitoring, the Sponsor's representative will ensure that the study staff makes necessary corrections directly to the CRF(s) prior to collection.

Following CRF collection, the Sponsor will review the data. A Data Clarification Form (DCF) may be provided to the site to correct or clarify discrepancies.

If a site discovers discrepancies after CRF collection, the site may notify the Sponsor and request data modification.

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 Principal Investigator or institution shall provide direct access to source data during and after the clinical investigation for monitoring, audits, EC review, and regulatory authority

inspections. The source data available to the Sponsor will include the original ABUS images, any screen-based images, and associated acquisition protocols.

11.1.4 Archiving

All study data must be archived for a minimum of 2 years after study termination or premature termination of the clinical trial, in accordance with applicable laws and regulations. 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 investigator agrees to affirm and uphold the principle of the participant's right to privacy, and the investigator 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, a competent authority (CA), or an ethics committee (EC) 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

Electronic 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, used, and disclosed by the Sponsor indefinitely. The PI as well as 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, with agreement from the PI and the Sponsor. The conditions of publication are described in a separate contractual agreement.

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APPENDIX A – STUDY SITE AND INVESTIGATOR LIST

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

[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]

[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***.

[redacted]

APPENDIX B - AMENDMENTS (PROTOCOL VERSION 1.0 TO 2.0)

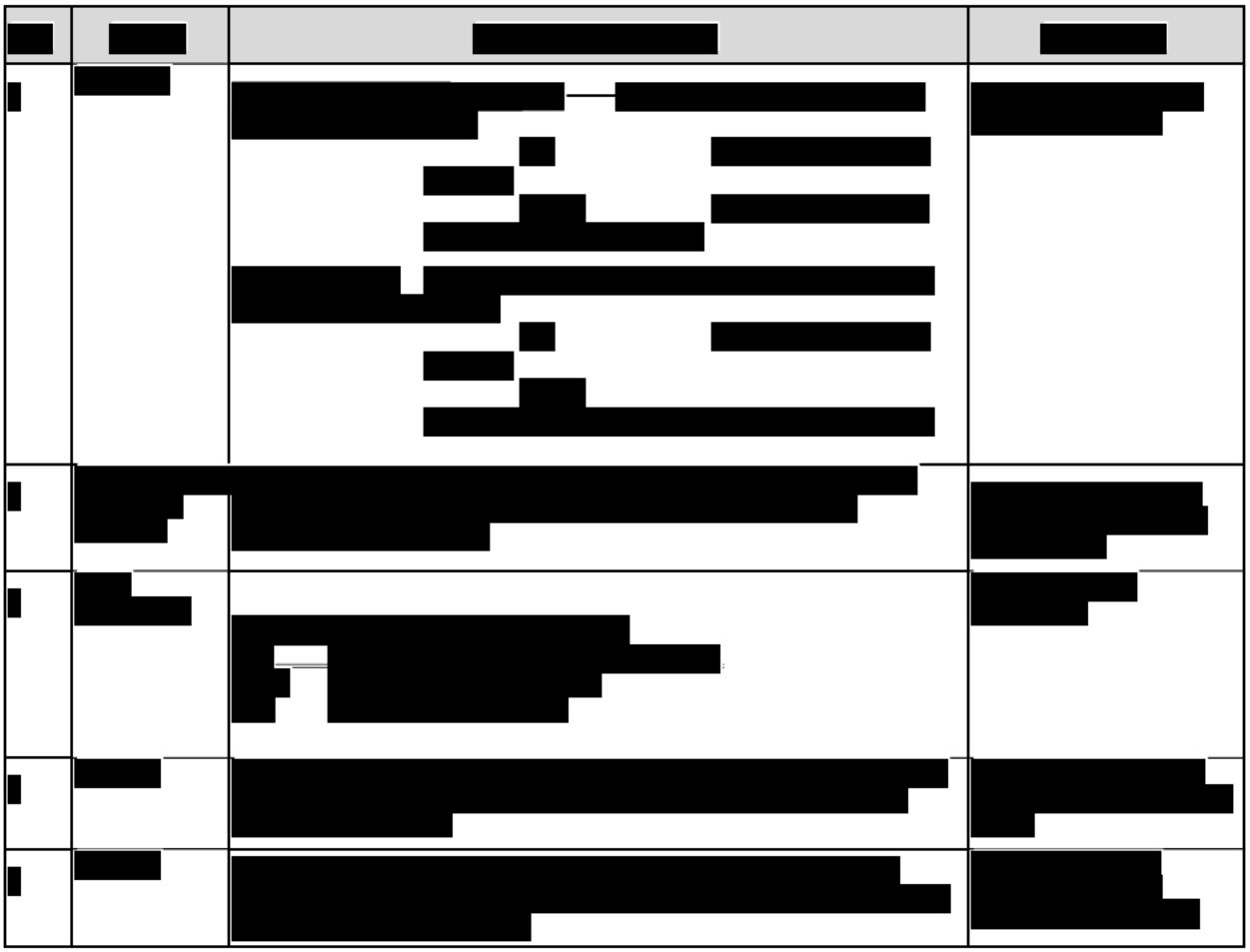
Purpose of Amendment:

This amendment document describes the changes from protocol version 1.0 to 2.0, as follows:

1) To update Sponsor Contact and Medical Monitor and their contact information.
2) To correct paraphrasing and add appropriate citations to the Background and Justification section.
3) To remove FFDM as a mandatory part of the procedure, and include it as an optional procedure.
4) To increase sample size from 2,000 subjects to 10,000 subjects.
5) To adjust follow up for the study, allowing for follow up after a year.
6) To update Investigators, sites, and corresponding contact information.
7) To make general typographical/formatting corrections, in accordance with current standard style guides, American Medical Association (AMA) style, and internal standards of the Sponsor.

These changes are not expected to increase subject or operator risk or to adversely impact the scientific integrity or conduct of the study.

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



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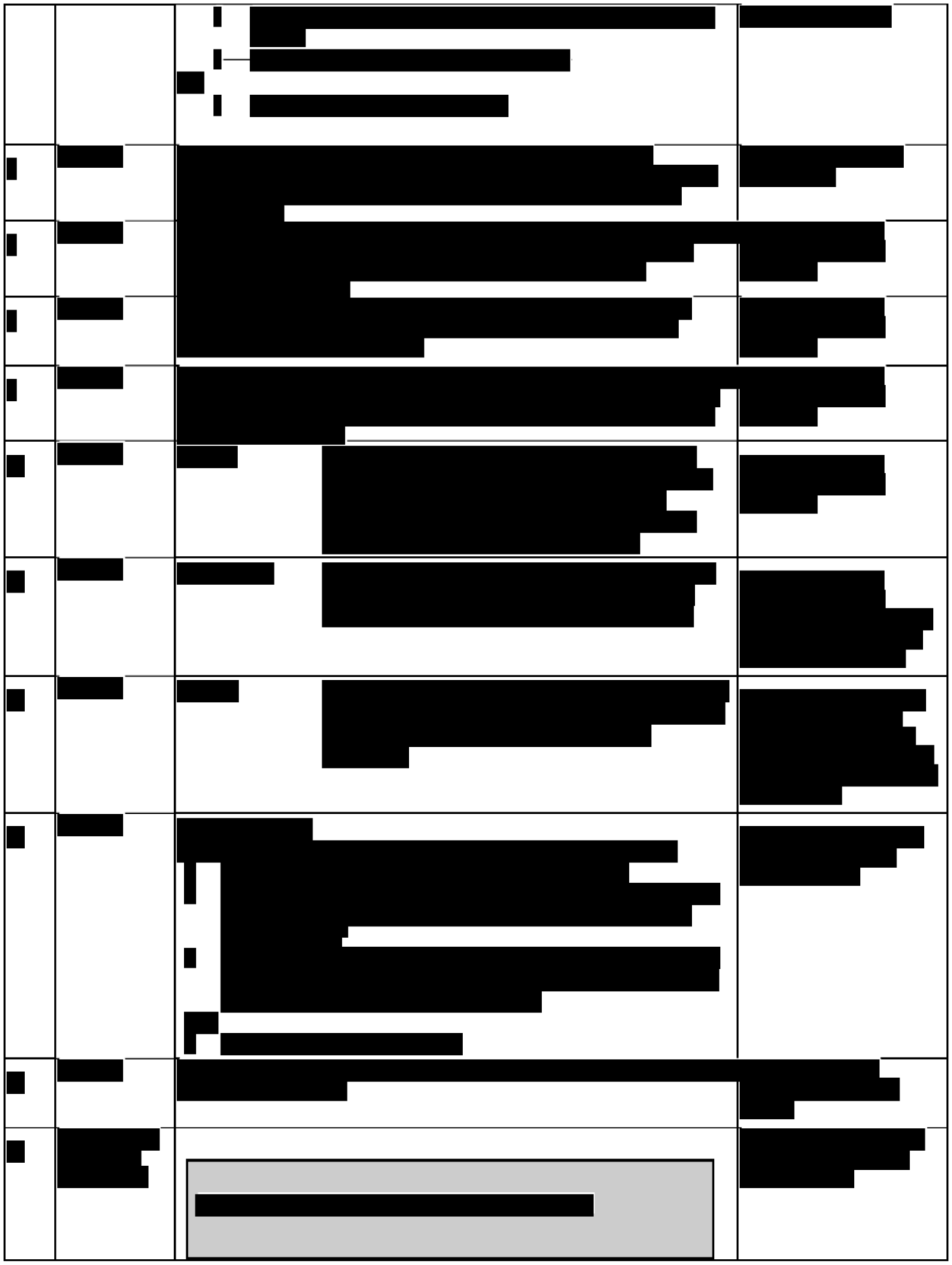

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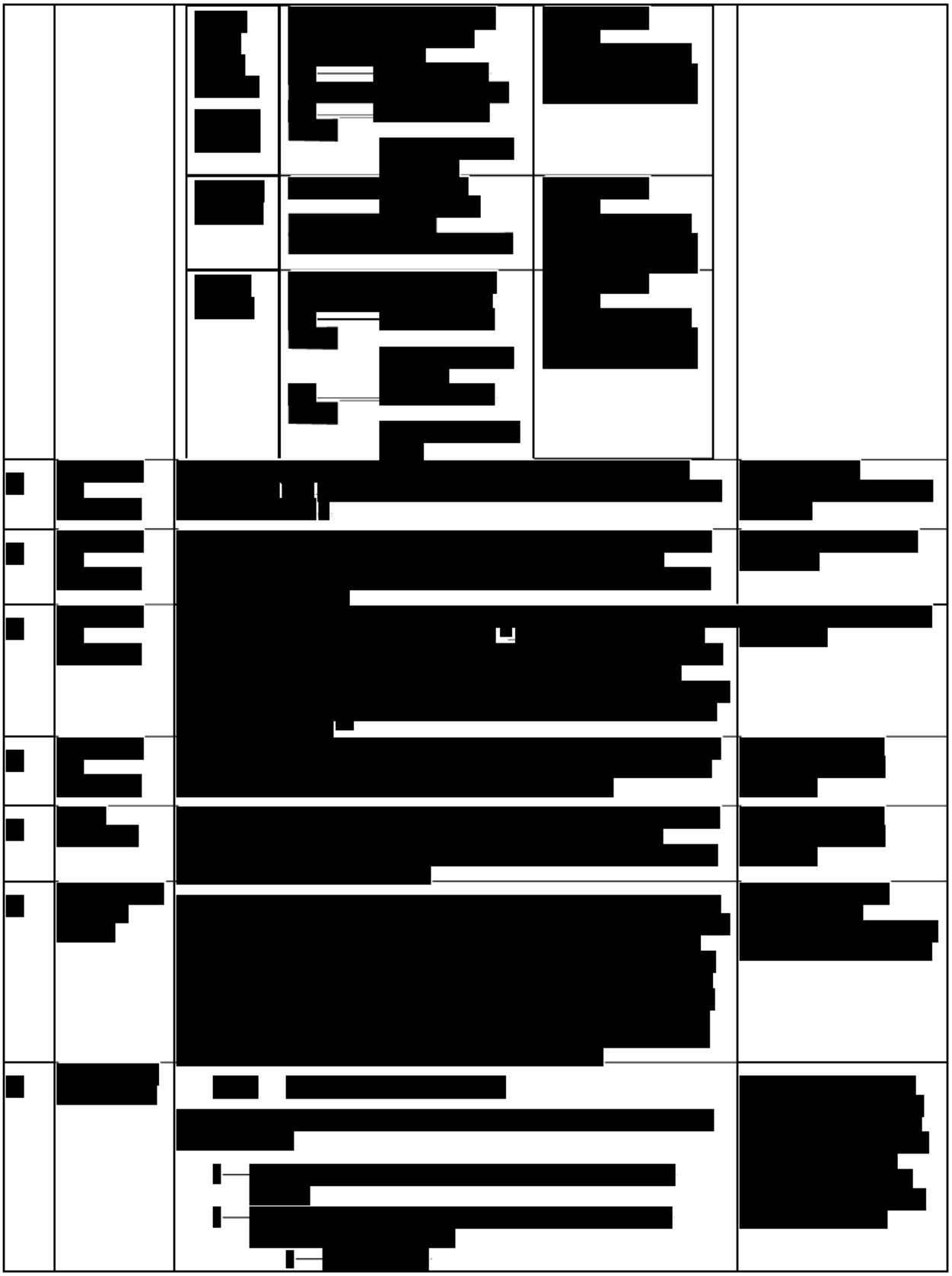

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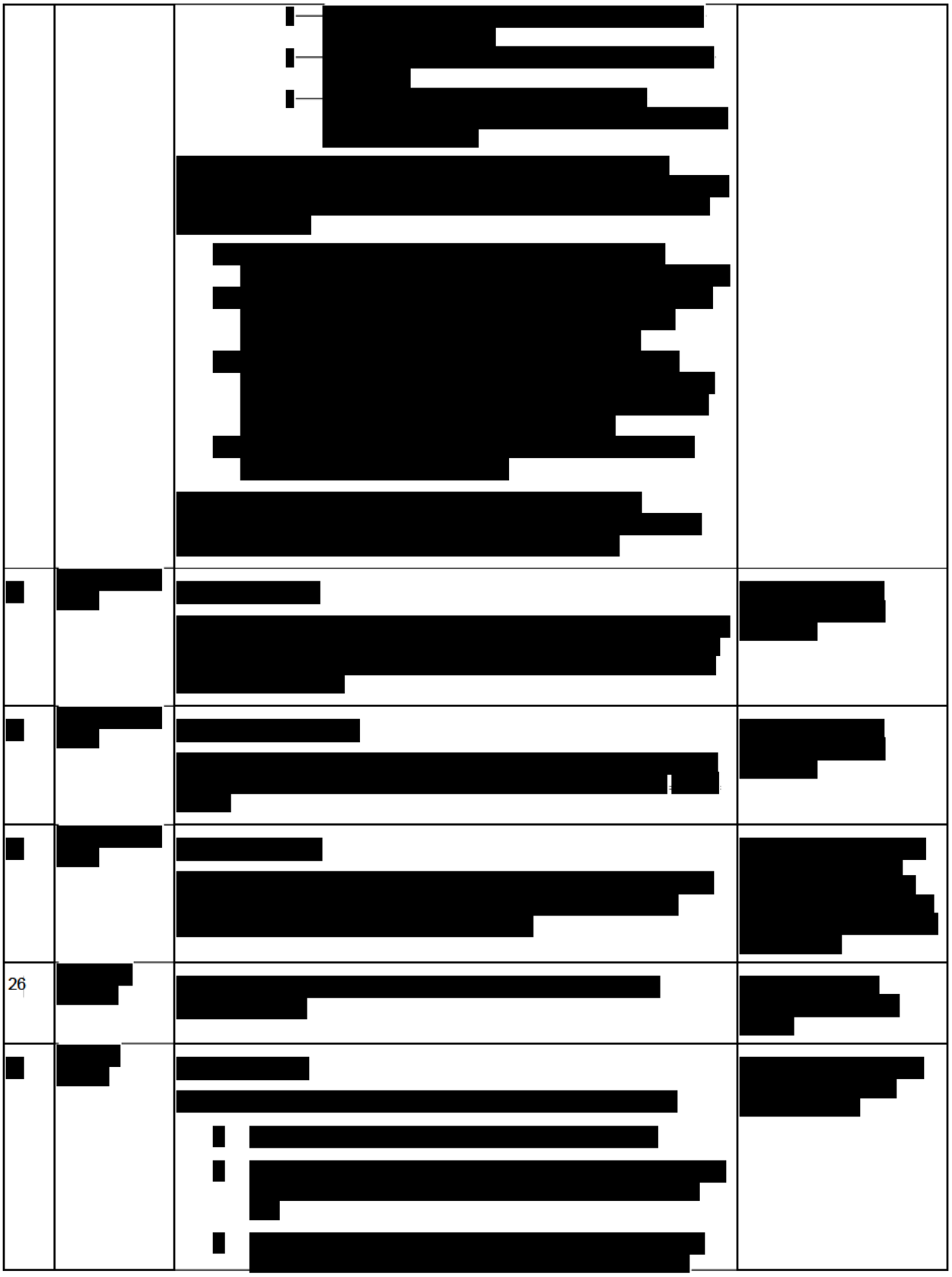

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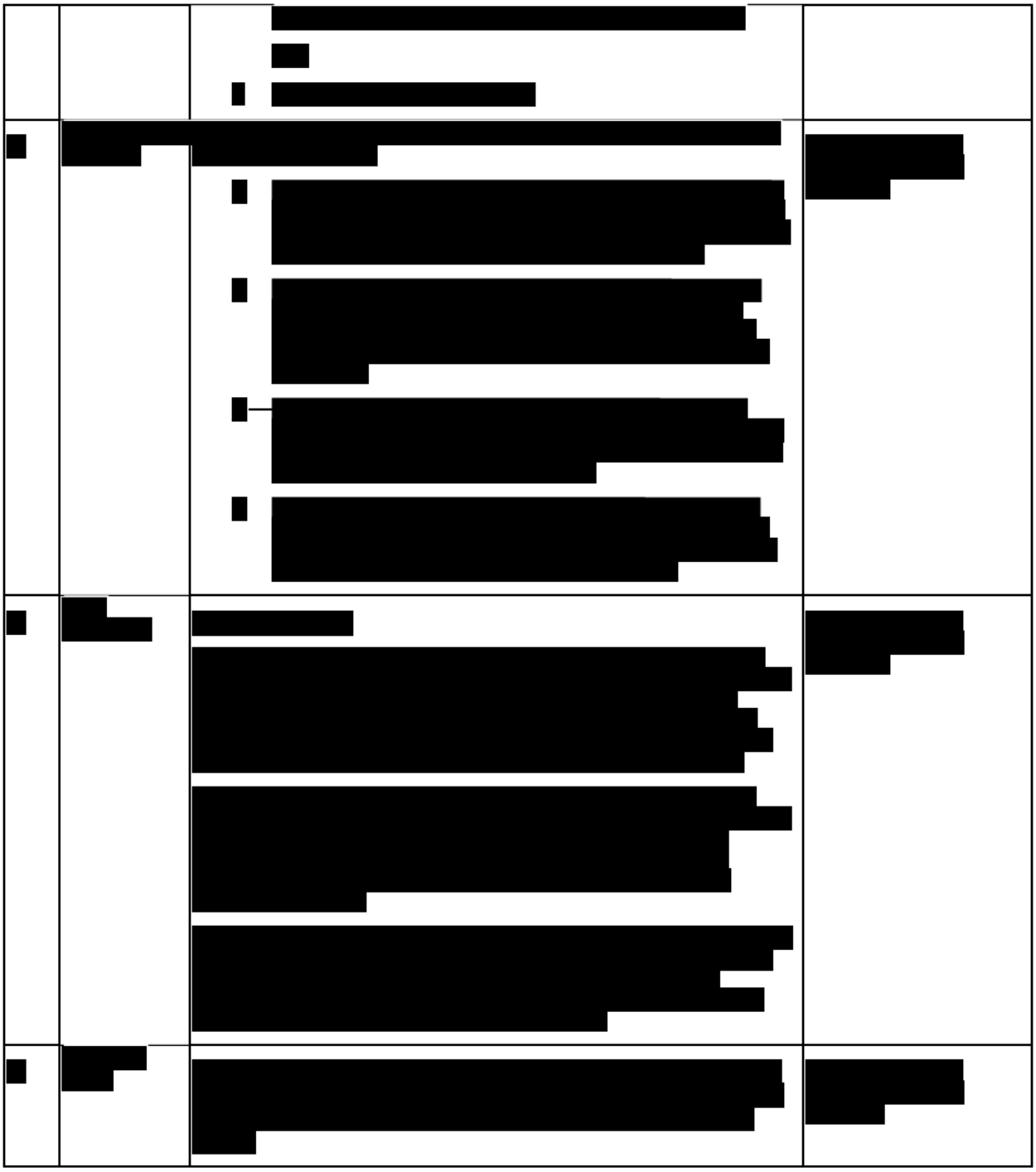
Study Title: Automated Breast Ultrasound Case Collection Registry
Study No: 110.01-2016-GES-0001



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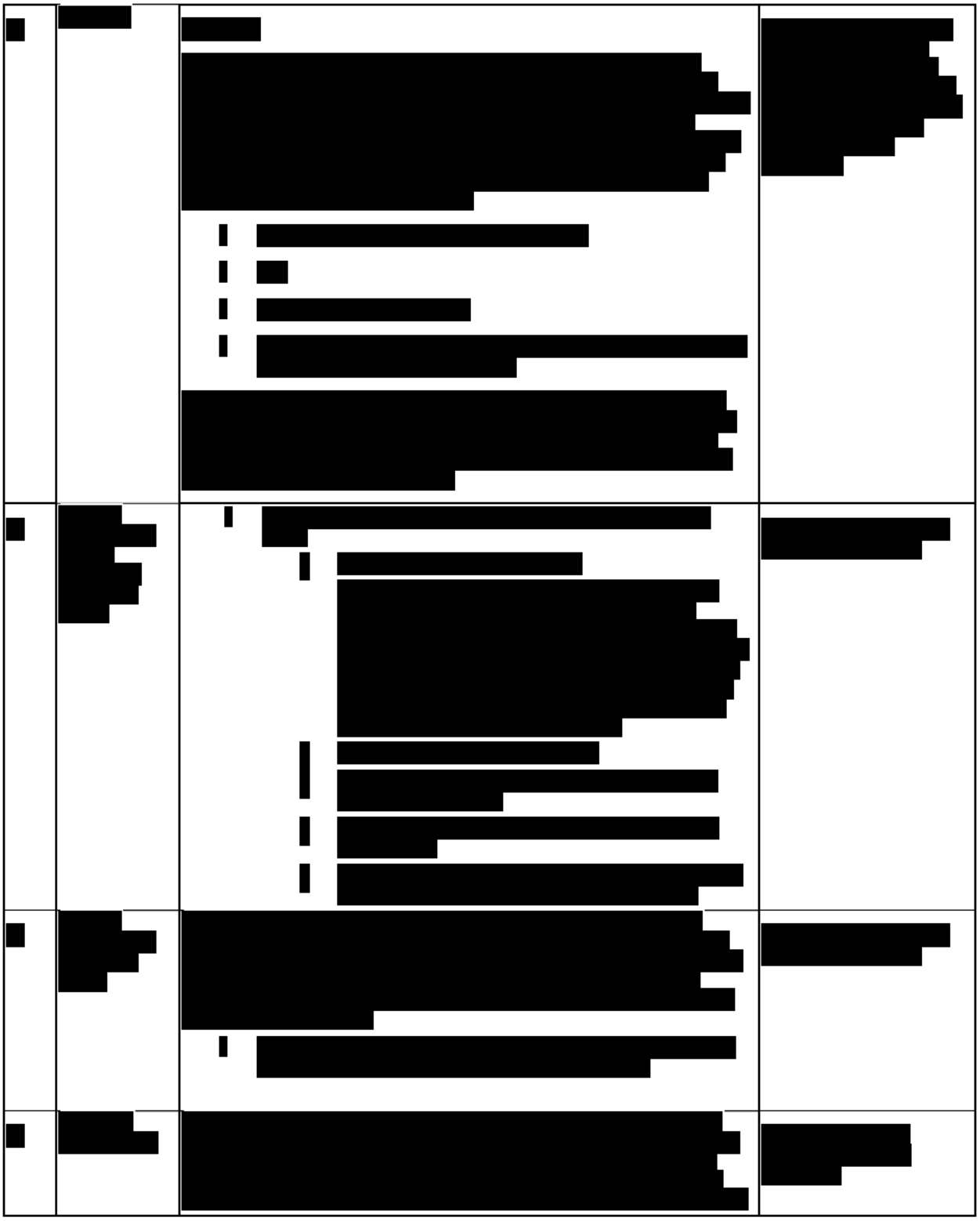

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APPENDIX C - AMENDMENTS (PROTOCOL VERSION 2.0 TO 3.0)

Purpose of Amendment:

This amendment document describes the changes from protocol version 2.0 to 3.0, as follows:

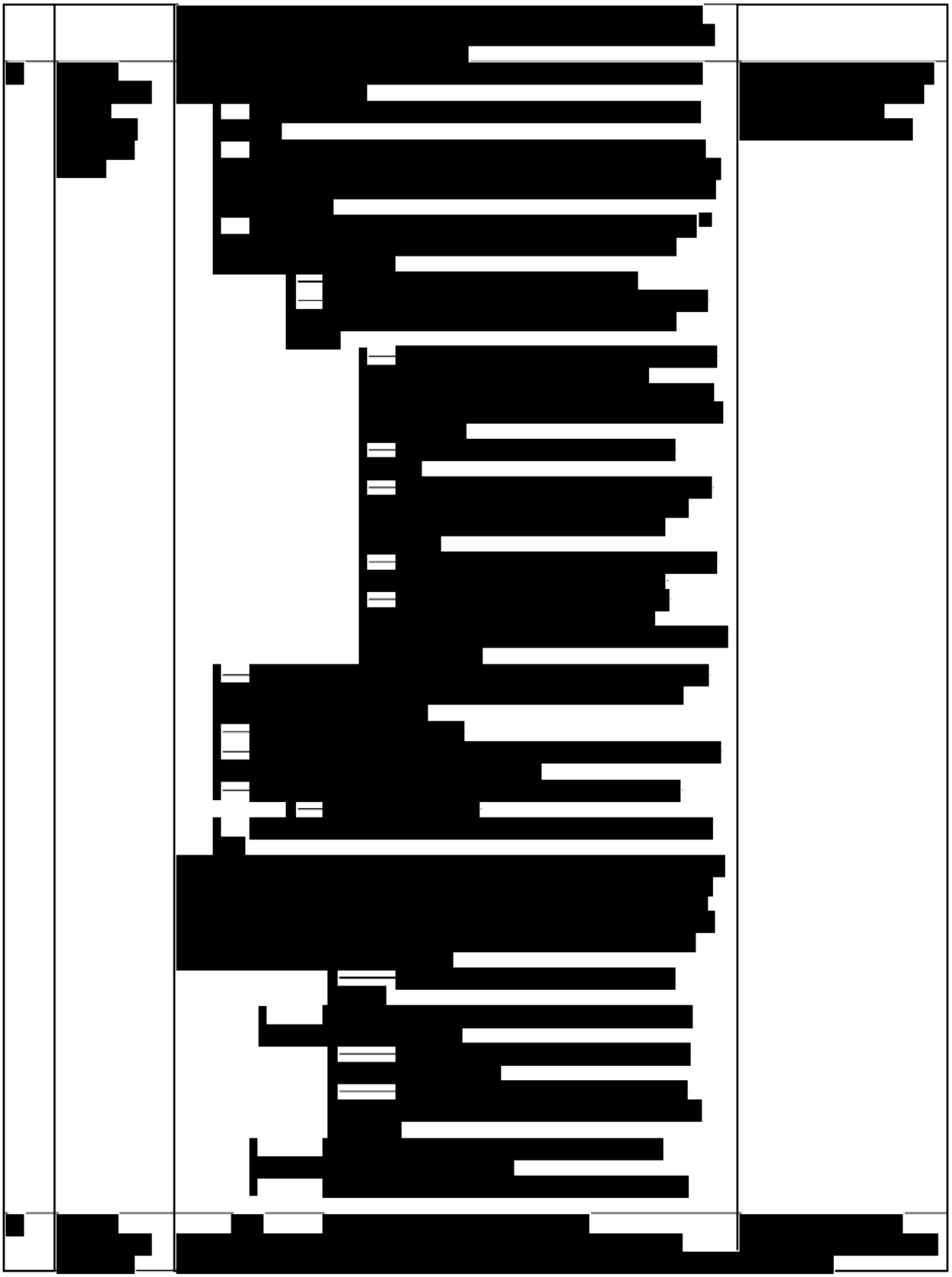
1) To update, clarify, and streamline data collection information regarding image reads, breast cancer status, and follow-up exams.
2) Correct time frame for archiving data.
3) Remove site and site information.
4) To make general typographical/formatting corrections, in accordance with current standard style guides, American Medical Association (AMA) style, and internal standards of the Sponsor.

These changes are not expected to increase subject or operator risk or to adversely impact the scientific integrity or conduct of the study.

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
[redacted]	[redacted]	[redacted]	[redacted]

[redacted]



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