Clinical Utility Study of a Low-Cost Hand-Held Breast Scanner

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1 Introduction

This document is a protocol for a human research study. This study is to be conducted according to US and international standards of Good Clinical Practice (International Conference on Harmonization ICHE6), the Code of Federal Regulations Title 21 parts 803 and 812, and other applicable government regulations and Institutional research policies and procedures.

1.1 Background

Breast cancer is a leading cause of cancer related deaths amongst women in Pennsylvania as well as in the US. Early detection improves the survival rate, makes treatment less costly and lowers the overall burden of the disease. Of note, Breast cancer (BC) is the most common cancer in women worldwide, disproportionately affecting low- and middle-income countries (LMICs):

- Today, 52.6% of new breast cancer cases occur in LMICs, and this is expected to grow to 70% by year 2020.[i]
- Two-thirds of the estimated 15,000,000 healthy-life years lost annually to breast cancer globally are from LMICs.[ii]
- 5-year survival is 40-60% in most LMICs as compared to 80-90% in High Income Countries (HICs).[iii]

Lack of secondary prevention programs (population based screening) and enhanced treatment, are the two major differentiating factors for poorer breast cancer outcomes in LMICs. Tumors detected as a result of routine screening tend to be smaller, well differentiated and less likely to have regional lymph- node involvement, making treatment more effective and survival more likely.[iv,v,vi] Smaller, earlier-stage tumors are amenable to better, less costly treatment options. The National Cancer Institute-supported Cancer Intervention and Surveillance and Modeling Network (CISNET) suggests that 28–65% (median 46%) of the observed decrease in BC mortality in USA can be attributed to screening, with the remainder attributed to adjuvant treatment.

1.2 Challenges with secondary prevention and early diagnosis of breast cancer in LMICs

In HICs, screening mammography and clinical breast exam (CBE) are the standards of care for BC screening and detection. Their efficacy, cost-effectiveness and effect on survival and mortality of BC have been well documented. However, availability and/or use of these modalities remain limited in LMICs.

Organized screening mammography is expensive, resource intensive, requires stringent quality assurance and a large, well-trained workforce of technicians and radiologists. The cost per year of life saved ranges between Int.$3,468 and Int.$16,000,[vii viii] which is beyond the health spending capabilities of most LMICs. In terms of human resources, most LMICs simply do not have the radiology expertise capacity required for an effective mammographic screening program. India, for example, has 10% the number of radiologists of the U.S. but almost 4 times the population.[ix] Clinically, mammograms are limited in women with dense breasts, which includes most women under 50 years of age. Culturally, in LMICs there are reservations about radiation based, sometimes painful mammogram tests.[x] So even when mammography is available, it is often not utilized; Mexico's Ministry of Health reports that only 25% of the installed mammography units are in use.[xi]

CBE. The World Health Organization and the Breast Health Global Initiative recognize CBE as a cost-effective measure to screen for BC in LMICs. In a study in Indonesia, CBE performed nearly as well as single-view mammography.[xii] In an IARC-supported, cluster-

randomized controlled study in India, CBE has been shown to enable the detection of early-stage breast cancers.[xiii] It is known however that the efficacy of CBE may be substantially lower (28-36%) in practice than is reported in clinical trials.[xiv] Physical exams in community health practice are often less systematic and poorer quality than in many organized clinical trials.[xv] So the true contribution of CBE to BC detection in healthy women, and to improved survival in BC patients, has come under question, resulting in recent calls to standardize and lower the subjectivity of CBE administration and reporting.[xvi]

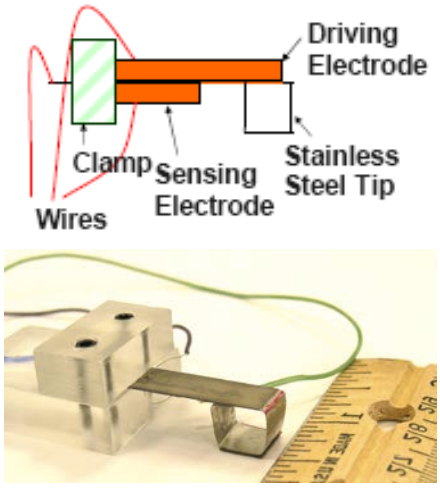
1.3 Health worker led "earlier detection"

The American Joint Committee on Cancer (AJCC) staging system indicates prognosis based on the size of the tumor at detection viz. stage of breast cancer. Identifying tumors at earlier stages (down-staging) can improve survival, assuming high-quality treatment is accessible. In the U.S., approximately 40 million women receive mammograms annually and roughly 232,000 new cases are identified; vast majority are detected at stage Tis and T1 with a 5-year survival of 100%. In the context of LMICs, where up to two-thirds of breast cancer cases present at late stages, systematic down-staging is required, such that majority of the cases would be identified at Stage II or earlier, where survival can be 93% or better (again, assuming treatment is available).

In LMICs, health workers, nurses and midwives represent the most affordable resource to bridge the accessibility gap due to the lack of secondary prevention programs like in HICs. What is needed is a low-cost, user-friendly technology that can be used by health workers with minimal training to administer standardized breast exams without any special infrastructure with the goal to down-stage breast cancer to at least Stage II. The low-cost technology must perform with better detection sensitivity than CBE (higher than 50%) and equally high specificity as CBE (94%) to accurately and effectively identify breast lumps in need of further diagnostic follow-up (diagnostic ultrasound, breast biopsy) without clogging the under-resourced infrastructure with false positives due to typical benign breast features (tissue variability, lumpiness and nodularity).

Contrast in elastic stiffness between normal and abnormal breast tissue has long been recognized (Harris '94). Breast cancers are known to be stiffer than normal breast tissues. Major medical device manufacturers are exploring different sensing mechanisms like Ultrasound Elastography and MRI, which use tissue stiffness to differentiate between malignant and non-malignant tissue.

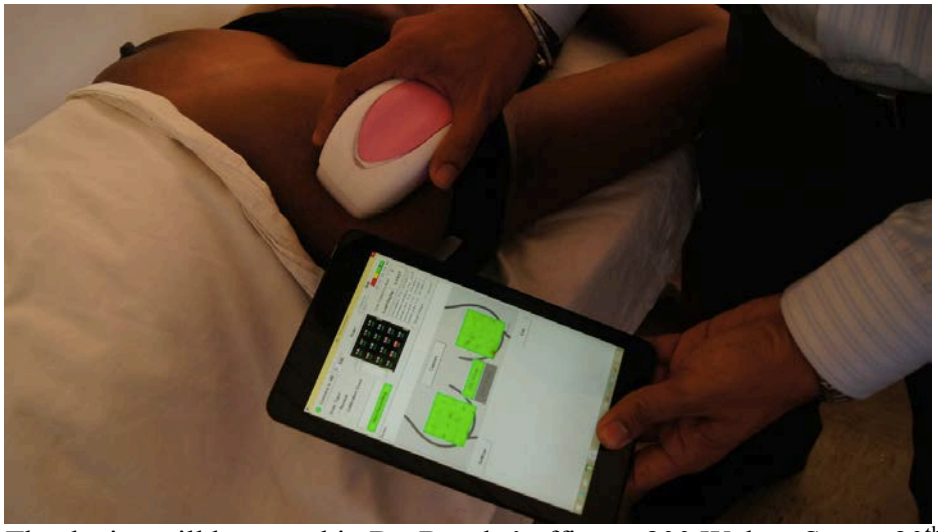
1.4 Investigational Device



The Piezoelectric Finger (PEF, Fig1), invented by Dr. Wan Shih and Dr. Wei-Heng Shih at Drexel University is a novel, quantitative and low-cost elastic modulus (E) sensor that can measure tissue compression by simple electrical means. PEF's ability to apply a force and measure the displacement electrically, all within the finger, makes for an ideal "electronic palpation" sensor for *in vivo* breast tissue imaging. Detection of abnormal breast tissues (e.g., carcinoma in situ, intra-ductal carcinoma, lobular carcinoma, etc.), and benign growths (e.g., fibrocystic lesions, hyperplasia, and calcifications) can be achieved by performing an E scan. The size and depth of the abnormal breast tissue can also be calculated using adjacent fingers.

Figure 1

The current PEFS system (Product Name: Intelligent Breast Exam™ or iBE™, Fig. 2) consists of a hand-held compression probe containing a 4 x 4 array of PEFS, a custom built electronics board and a tablet. iBE communicates wirelessly with a mobile device to display the findings in real-time, to store and share the data digitally and to easily compare the results with past records. iBE has the potential to 'optimize' CBE by improving on its overall effectiveness to detect Stage I and IIa breast cancers with minimally trained health workers. iBE will also 'standardize' breast exams by assisting every health worker to administer and record breast exams objectively, consistently and with the ability to share the results easily using the mobile device app.



The device will be stored in Dr. Brooks' office at 800 Walnut Street, 20th floor, Philadelphia, PA, 19107.

1.5 Feasibility Testing

1.5.1 Proof-of-Concept:

Early testing was performed using tissue models as part of the development of the proof-of-concept device. This testing included characterization of the device, establishing its ability to distinguish smooth and rough surface characteristics of benign and malignant tumors, and determining its depth limit *ex vivo* and *in vivo*. I

1.5.2 Ex-Vivo Tissue Testing:

We conducted testing on 71 *ex vivo* breast tissue samples under an IRB-approved protocol and compared PEF results with the pathology reports. Of the 71 cases, there were 33 cases of invasive cancer (32 cases of invasive ductal carcinoma and 1 case of invasive lobular carcinoma), 9 cases of ductal carcinoma in situ (DCIS), and 19 cases of benign conditions including fibrocystic, hyperplasia, calcifications, fibroadenoma, papilloma, and glandular tissues. The E values at the malignancies were 3-5 times those of areas of the normal breast tissues regardless of patients' ages.

1.6 Clinical Data to Date

***In Vivo* Testing**: Forty *in vivo* evaluations of the 1x4 PEF-compression probe were conducted by Dr. Ari Brooks at his Hahnemann Hospital outpatient office under an IRB-approved protocol. These evaluations were performed for device development, not clinical utility. The probe was tested with various pushing depth, i.e., at 2 mm, 4 mm, or 6 mm pushing depths to assess the effect of different pushing depth on the measured elastic modulus map. The results showed that different pushing depths did not alter the tissue elastic map, in terms of the lesion location and size. The PEF measurements were compared to patients' mammography reports. All tests were blinded.

A total of 40 patients were enrolled and 46 lesions were confirmed by imaging or pathology. PEF reported 55 lesions, with 9 false positives and 2 true positives not originally found on imaging or palpation. The overall sensitivity of the PEF test was 40/46 or 87%. In women 40 years or younger the overall sensitivity was 19/19 or 100%. In women who had a lesion visible on mammography, PEF had a sensitivity of 83% (24/29). Of these, in women aged 40 or younger, PEF identified all 7 mammographically visible lesions, including 2 malignant lesions. When compared with ultrasound, PEF correctly identified 87% (34/39) in this group. Of these, in women aged 40 or younger, PEF identified 100% (19/19) of all ultrasound visible lesions.

UPenn Clinical Pilot Study
A total of 44 patients were enrolled in this prospective signal processing/algorithm development trial. Patients presenting to the Pennsylvania Hospital Women's Imaging Center for breast diagnostic services including ultrasound and/or diagnostic mammogram and/or needle biopsy were recruited for an iBE exam prior to biopsy. The final production prototype device was used for all studies.

The demographic result of the patient population is 59% Caucasian 34% African Americans, 2% Asian, and 4.5% unknown with an average age of 41 with one male having participated in the study. The patient population is comprised of those who needed breast diagnostic services of the 44 patients 50% were determined to be BIRADs 2, and the other 50% were BIRADs 3 or 4, zero patients were categorized BIRADs 1 or 5. 17 subjects of underwent a biopsy.

1.7 Risk/Benefits

The piezoelectric finger (PEF) is a battery powered, electrically insulated device and poses very little risk of electric shock to subjects. The maximum voltage is 5V and the maximum current is 1 mA, both of which are safe to humans. The PEF presses gently on the breast causing negligible discomfort, similar to an ultrasound exam. The subject may feel the contact of the polycarbonate holder without discomfort, and once the polycarbonate holder is in position, the PEFS will compress a maximum of 35 microns, which the subject will not be able to feel. In conclusion, PEFS will pose minimal risk to subjects with negligible discomfort.

This study will provide no direct benefit to subjects and there may or may not be any direct benefit to society. In the future, possible benefits to others include the ability for patients, for whom mammography is less effective or not available, to be screened for cancer.

2 Study Objectives

The company that has licensed the technology has received funding to develop a low-cost, reliable, and commercially viable device for screening individuals who don't have access to the benefits of mammographic screening. This device is called the iBE (see Section 1.2).

The goal of this research project is to measure the accuracy of the iBE device for detection of clinically relevant findings in the breast. This study would establish a validated sensitivity and specificity for breast lesion detection using the results of current mammography based breast screening. These results are needed in preparation for an international trial of the device in Low-Middle Income Countries. This research project will have no impact on clinical decision making.

3 Study Design

3.1 General Design

Determination of the accuracy of iBE for the detection of clinically relevant breast lesions will be performed by means of a prospective study. Subjects may participate during a previously scheduled visit to the women's imaging center. All women presenting to the imaging center, including screening, diagnostic or interventional procedures, will be eligible for participation. A subset of patients will undergo dual examinations by different trained individuals with the results compared for inter-rater reliability.

The estimated date for the investigators to complete this study (complete primary analyses) is approximately 2 years from study activation.

3.2 Study Endpoints

- To determine the sensitivity and specificity of iBE exams for the detection of clinically relevant breast lesions (defined as BIRADs 3-5 on imaging, and/or malignant on biopsy).
- To determine inter-rater reliability in the iBE production prototype.

4 Subject Selection

4.1 Inclusion Criteria

- 18 years of age and older
- Women and men with symptomatic breast lump (either by palpation or imaging) OR
- Asymptomatic women presenting to the imaging center for a screening mammogram.
- Signed Informed Consent

4.2 Exclusion Criteria

- Patients under 18 years of age
- Patients who previously participated in this study and are returning to the Women's Imaging Center for follow-up diagnostic tests

4.3 Subject Recruitment and Screening

Subjects will be offered participation in the study during their visit to the Women's Imaging Center by the PIs, Dr. Ari Brooks, Dr. Brian Englander, and/or their designee. This study may recruit up to 1000 subjects. Patient's will be eligible for study participation if they have a scheduled visit for the Women's Imaging Center and have not previously participated in this study. The reason for the patient's visit, screening or diagnostic, will not affect their eligibility. Diagnostic visits are included as it is necessary to ensure the accuracy of the iBE device's ability to detect BIRADs 3-5. The iBE device was created to use as a screening tool to detect clinically relevant breast lesions, defined here as BIRADs 3-5, with the purpose of giving patients proper follow-up recommendations without causing unnecessary anxiety of avoidable diagnostic tests.

5 Study Procedures

Participants will be recruited from the Women's Imaging Center who are scheduled to undergo screening or diagnostic imaging including biopsies. Subjects will have the study explained to them and given the consent form to review early in their imaging center visit. After the subjects have had time to review the consent, the PI or designee will answer all questions. If she/he agrees and signs the consent form, they will receive a signed copy to take home with them. All subjects must meet the inclusion and exclusion criteria. Consent will be obtained prior to any study-related activities.

The iBE evaluation will be performed by a trained individual who is blinded to the outcome of the radiology studies at the time the iBE is performed. The trained individual will be a healthcare worker with minimum education (or equivalence) to a licensed practical nurse (LPN) or an ultrasound tech. This is the target education level for the intended iBE operators. The selected healthcare worker will be trained by Dr. Ari Brooks, MD to administer the iBE and clinical breast exams. The trainee will follow Dr. Brooks during clinic hours for 1-2 days and trained for clinical breast exams, similar training to a medical student. The iBE training will mostly be software and instrument training by the leading iBE user in the United States, Dr. Brooks. A minimum of two healthcare workers will be trained.

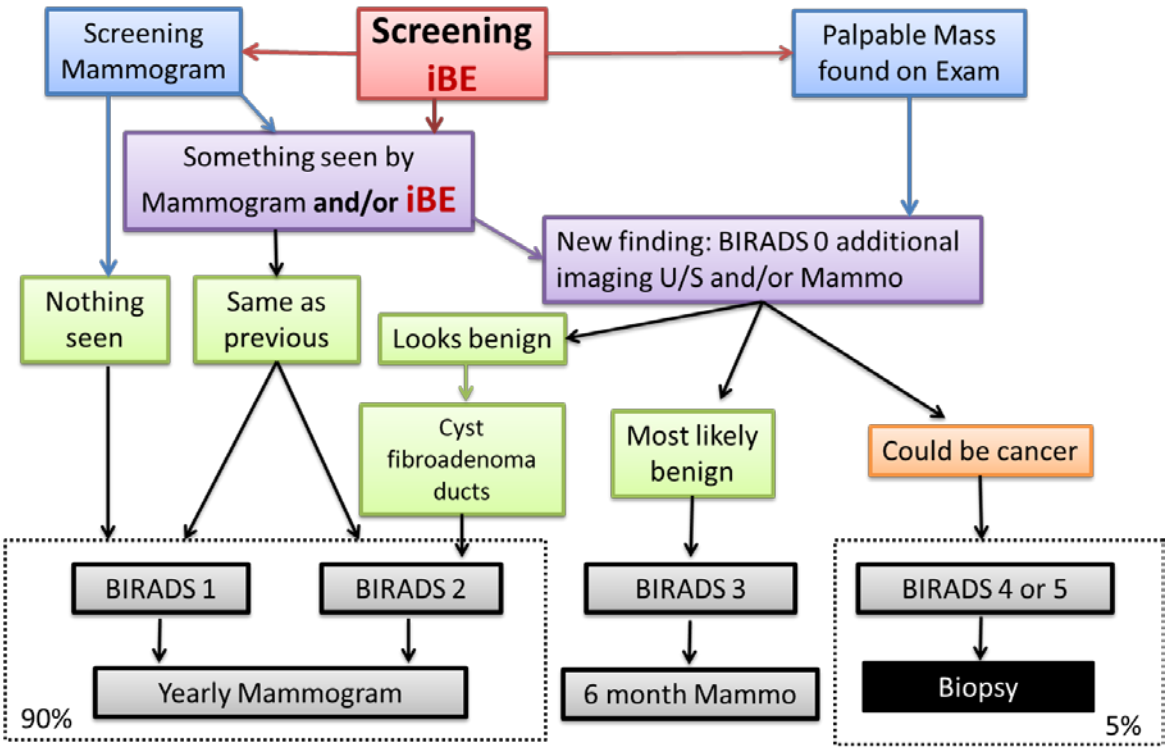
Subjects will be scanned with the iBE device administered by the trained individual while in a supine position without breast immobilization similar to ultrasound testing. A bilateral iBE exam will be performed on the entire breast as well as a bilateral Clinical Breast Exam (CBE) the findings will be documented on the case report forms and the device tablet concurrently.

If the patient is selected to participate in the inter-rater reliability portion of the study, the subject will undergo both the iBE and the clinical breast exams twice performed by two different separately trained individuals sequentially during the same visit. The trained individuals will have their own case report forms and tablets that integrate to the iBE to prevent results sharing and bias. The selection for the inter-rater reliability portion of the study will be decided by the day of the week. The second trained individual will be present one a day week and that day all the patients will be asked to participate in the dual exam inter-rater reliability portion of the study.

These data are recorded and processed by an automated software algorithm and the results are displayed topographically on a "breast-map" with red areas showing positive findings and green areas showing negative findings. All the recorded data are collected on the tablet without HIPAA identifying variables. The tablet will assign a four digit subject number incrementally increasing for each subject prior to the iBE scan and this number will be recorded on the case report form. Results of the test will be reported to the patient as well as the radiology technologist and radiologist. The iBE evaluation may add between 10 and 30 minutes to the clinic visit. The iBE evaluation will be done prior to the patient's original scheduled imaging visit. After the completion of the imaging visit the radiologist will evaluate the images and the iBE report. If there are areas identified on the iBE that are not resolved by the scheduled mammogram an ultrasound will be performed in the area of concern (if not already scheduled).

The current pathway of breast lesion detection can be modified in this protocol in order to ascertain the accuracy of the iBE device illustrated in Scheme 1 below. The current pathway of breast lesion screening and detection begins with a screening mammogram or a diagnostic mammogram/ultrasound. If nothing is detected by mammogram or ultrasound then the pathway is complete and a follow-up recommendation is given. However, if something suspicious is detected by the initial mammogram then additional imaging is requested such as an ultrasound. If the additional ultrasound reveals something suspicious a biopsy maybe recommended for confirmation or if a benign finding is revealed a follow-up recommendation is be given. The addition of iBE screening will only modify the current pathway if the iBE exam returns a positive result when the initial mammogram provides a negative result. If this occurs a study provided ultrasound will be recommended and the ultrasound's results will be used to verify the iBE positive result. If the ultrasound invalidates the iBE positive result, it will be deemed a false positive and the diagnostic tests are complete. However, if the ultrasound confirms the iBE's result Dr. Brooks and the radiologist will discuss if further diagnostic intervention (i.e. biopsy) is required. Data on the final disposition of the imaging, any biopsies and any follow up imaging to 18 months after participation will be recorded in the database.

Scheme 1: Current Algorithm with Integrated Study Pathway



Quantitative Data

Quantitative data from the test will be documented and analyzed for accuracy metrics.

The iBE device collects only compression measurements and stores these data on the mobile device. Compression data are recorded for our records and a copy is available to UELS via Dropbox, which is backed up online and offsite.

We know the data are captured accurately because a unique file gets created at the end of every scan in a specific folder inside the DELL tablet. The app gives the user a notification that the data were saved properly to the tablet at the end of each scan.

The data sent to the UELS database are identical to those on the tablet, as they are synced between the folder inside the tablet and Dropbox. This ensures that an exact copy of the files created at the site are sent to UELS. These files use a unique ID entered by the user and have no identifiable patient information.

No identifiable data are collected or stored by the iBE software. iBE data are stored at UELS on an encrypted database. All data that are transmitted are de-identified and sent directly to the database from the device. Each study performed on the device has a unique number. The unique

study numbers are entered into the database at Penn and associated with a subject number. The results of the clinical breast exam are recorded on the touch screen in a similar heat map fashion.

Other data associated with each subject number includes age, bra size, BMI, and breast lesion location. In symptomatic individuals, imaging results, final diagnosis, type of lesion, imaging and pathology data will be collected on a separate CRF and entered in the Penn database.

The data listed above as well as identifiable demographic data will be entered into a REDCap database that is only accessible to the research team. The original signed consent documents and CRFs are kept in a locked office at 800 Walnut Street, 20th floor.

6 Statistical Plan-Paul's expertise

6.1 Sample Size Determination

Based on a study of BIRADS grading of a mammography registry, 80% of all screening mammograms are BIRADS 1 and 2. The incidence of malignancy should be 1-2% of all screening mammograms. The screening center performs 11,000 screening mammograms a year plus over 3000 biopsies. About 600 breast cancers are diagnosed yearly. Since symptomatic individuals scheduled to undergo diagnostic imaging or biopsy are eligible to participate this will enrich the population categorized to BIRADs 3-5. Using a sample size of 1000 subjects provides 80% power.

6.2 Statistical Methods

Data will be analyzed using contingency table methods, estimating the sensitivity and specificity of the device to correctly assign subjects to BIRADS 1, 2 versus BIRADS 3, 4, 5 categories. Sensitivity is calculated from contingency table counts as TP/(TP+FN), and specificity is calculated as TN/(TN+FP), (and will be log transformed) with variances obtained using the delta method. Both sensitivity and specificity measures are expected to be high, given great performance in preliminary data (0.95 and 0.92 respectively). We will use a non-inferiority approach, attempting to demonstrate that in the clinical setting, iBE matches our preliminary values, and we will test them against null hypothesis values (Non inferiority boundaries) that are 5% below our preliminary data using the z-score for the log-transformed measure.

	Mammogram BIRADS 1,2	Mammogram BIRADS 3,4,5 or biopsy positive (same breast and same quadrant)
iBE negative	True Negative (TN)	False Negative (FN)
iBE positive	False Positive (FP)	True Positive (TP)

And to CBE as a primary comparison

	CBE negative	CBE positive
iBE negative	True Negative	False Negative
iBE positive	False Positive	True Positive

7 Safety and Adverse Events

Due to the nature of this device and our experience thus far, adverse effects are not anticipated, however, the investigator will follow the processes below should an event occur.

7.1 Definitions

Adverse Device Effect (ADE)
All adverse events will be graded using NCI Common Terminology Criteria for Adverse Events (CTCAE) v4.0. For the purposes of this study, an adverse device event (ADE) will be defined as any untoward medical occurrence following exposure to the PEFS device regardless of expectedness or attribution.

Unanticipated Adverse Device Effect (UADE)
An unanticipated device effect is 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 investigational plan, or any other unanticipated serious problem **associated with a device** that relates to the rights, safety, or welfare of subjects.

Serious injury
Any injury that is any one of the following:

- Life-threatening
- Results in permanent impairment of a body function or permanent damage to body structure
- Necessitates medical or surgical intervention to preclude permanent impairment of a body function or permanent damage to a body structure

7.2 Recording of ADEs
All events experienced by subjects or identified by the investigator that qualify as an ADE or UADE will be recorded in the medical records. The clinical course of each event should be followed until resolution, stabilization, or until it has been determined that study participation is not the cause. Serious ADEs (SADEs) that are still ongoing at the end of the study period must be followed up to determine the final outcome.

The minimum initial information to be captured in the subject's source document concerning the ADE includes:

- Study identifier
- Subject number
- A description of the event
- Date of onset
- CTCAE Grade
- Investigator assessment of the attribution to PEFS
- Investigator assessment of the expectedness of the event
- Current status
- Whether the event is serious and reason for classification as serious

7.2 Reporting of ADEs and Unanticipated Problems

7.2.1 Investigator reporting: Notifying the IRB

Unanticipated Problems Involving Risk to Subjects or Others

In alignment with 21 CFR 312, investigators are required to promptly report unanticipated problems, including suspected adverse reactions and adverse reactions, to the IRB. An event is considered a "suspected adverse reaction" when there is reasonable possibility that the drug/investigational product caused the adverse event. For these reporting purposes, reasonable possibility means there is evidence to suggest a causal relationship between the investigational device and the event. **For University of Pennsylvania IRB reporting, this means an event should be considered *probably or definitely related to the research procedures.***

The IRB requires investigators to submit reports within 10 working days (with one exception) of events that meet the definition of an unanticipated problem involving risks to subjects or others. Exception: If the adverse event involved a death and indicates that participants or others are at increased risk of harm, investigators are required to submit a report to the IRB within 3 days.

7.2.2 Investigator reporting: Notifying the Abramson Cancer Center Data and Safety Monitoring Committee (DSMC)

On-Site subjects (this includes any subjects enrolled at other sites on an in-house study)

1. All grade 3 or higher events (ADE or SADE) within 5 business days of knowledge
2. All unexpected deaths within 24 hours of knowledge
3. All other deaths within 30 days of knowledge. Deaths of subjects off-study for greater than 30 days from the last study treatment/intervention are not reportable with the following exceptions:

    a) Deaths on in-house gene or cellular therapies
    b) Deaths on in-house studies utilizing on-campus manufacturing of the study agent(s) or components of the study agent(s)
    c) Deaths on first-in-human studies

All events meeting the DSMC reporting requirements must be entered into the mandatory Velos AE/SAE form.

Every effort will be made to report an event as a **diagnosis**, not as a list of symptoms. Symptoms that led to the diagnosis should be included in the event description, but should not be the actual event.

7.3 Exceptions and Deviations

Exception
A one-time intentional action or process that departs from the IRB- and CTSRMC-approved study protocol, intended for one occurrence. If the action disrupts the study progress, such that the study design or outcome (endpoints) may be compromised, or the action compromises the safety and welfare of study subjects, advance documented IRB and DSMC approval is required.

Deviation
A one-time, unintentional action or process that departs from the IRB- and CTSRMC-approved study protocol, involving one incident and identified retrospectively, after the event occurred. If the impact on the protocol disrupts the study design, may affect the outcome (endpoints), or compromises the safety and welfare of the subjects, the deviation must be reported to the DSMC within 5 business days. The PI will document his assessment of the impact of the event on safety and/or study outcome integrity in a memo to file for each deviation.

7.3 Medical Monitoring

It is the responsibility of the Principal Investigator to oversee the safety of the study at his site. This safety monitoring will include careful assessment and appropriate reporting of adverse events as noted above. Medical monitoring will include a regular assessment of the number and type of ADEs.

8 Data Handling and Record Keeping

8.1 Confidentiality

Information about study subjects will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA). Those regulations require a signed subject authorization informing the subject of the following:

- What protected health information (PHI) will be collected from subjects in this study
- Who will have access to that information and why
- Who will use or disclose that information
- The rights of a research subject to revoke their authorization for use of their PHI

Subjects may withdraw permission to use and share their health information at any time and for any reason. Even if subjects withdraw permission, we may still use their information that was collected before their request if that information is necessary to the study.

8.2 Maintaining Records

Regulations require investigators to maintain all data/records for a period of 2 years after the date the investigation is completed or terminated or the records are no longer required to support a premarket approval (PMA), whichever date is later. Since the data/records from this pilot study will be needed to support a PMA for the clinical utility study, data/records for this study will be maintained for 2 years from the clinical utility PMA.

8.3 Source Documents

Source data are all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents.

9 Study Monitoring, Auditing, and Inspecting

9.1 Study Monitoring Plan

Safety and study quality will be monitored on an ongoing basis by the PI and the study team per the study-specific Abramson Cancer Center (ACC) monitoring plan submitted with this study protocol. The Principal Investigator will review all data for accuracy. Safety data will be collected at the time of the procedure. The PI or designee will review the study charts to evaluate events at each subject interaction to ensure the grade, relationship to the study device, expectedness and the course of action for each subject is documented.

9.2 Auditing and Inspecting

This protocol will be audited as a moderate risk study by the ACC Department of Compliance and Monitoring in accordance with the National Cancer Institute-approved Institutional Data and Safety Monitoring Plan. The investigator will permit study-related monitoring, audits, and inspections by the IRB, the sponsor, government regulatory bodies, and University compliance and quality assurance groups of all study-related documents (e.g., source documents, regulatory documents, data collection instruments, study data, etc.). Participation as an investigator in this study implies acceptance of potential inspection by government regulatory authorities and applicable University compliance and quality assurance offices.

10 Study Finances

10.1 Funding Source

UE Lifesciences, Inc.

10.2 Conflict of Interest

There are no conflicts of interest.

10.3 Subject Stipends or Payments

Subjects will receive a $10 cash card for participation in the study to compensate them for their time.

11 References

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