Protocol CTP-0005 v 2.0

June 30, 2015

XPAND II

AirXPanders AeroForm Tissue ExpaNDer System for Breast Reconstruction

A Prospective, Multi-Center, Single Arm, Open Label Continued Access Clinical Study

Investigational Device Exemption (IDE) # G110022

AirXpanders, Inc.

1047 Elwell Court

Palo Alto, CA 94303

Author: Kathryn Kelley, R.N., B.S.N., Director Clinical Affairs

Study Contacts

AirXpanders Inc.	1407 Elwell Court Palo Alto, CA 94303	www.airxpanders.com 650-390-9000 (Main) 650-390-9007 (Fax)
Daniel Jacobs, M.D.	Chief Medical Officer	jacobsdr@pacbell.net 650-303-6140 (Cell)
Kathryn Kelley, R.N., B.S.N.	Director, Clinical Affairs AirXpanders, Inc.	kkelley@airxpanders.com 650-390-9003 (Office) 650-390-9007 (Fax) 925-360-5173 (Cell)
SAE Hotline	24 Hour FAX	650-249-2200
Emergency Contact	AirXpanders (Main)	650-390-9000

Protocol Signature Page – Sponsor

Protocol:	CTP-0005
Study Title:	Air**XP**anders **A**eroForm Tissue Expa**ND**er System for Breast Reconstruction (XPAND II)
Study Device:	AeroForm® Tissue Expander System
IDE #:	G110022
Protocol Version:	2.0
Device Version:	Clinical Version 2.5
Study Sponsor:	AirXpanders, Inc.

This protocol was written and will be conducted in compliance with FDA Investigational Device Exemption (IDE) regulations (21CFR, Part 812) as well as those regulations governing Institutional Review Boards (21 CFR, Part 56), Protection of Human Subjects (21 CFR, Part 50), Financial Disclosure by Clinical Investigators (21CFR, Part 54), ISO 14155 for conduct of clinical investigations of medical devices including ICH Guidelines for Good Clinical Practice and any conditions of approval imposed by the FDA. Any changes or modifications to this protocol will be submitted for approval to the appropriate regulatory authorities and/or IRBs prior to implementation of the proposed changes.

Required Approval	Name	Signature	Date
Chief Medical Officer	Daniel Jacobs, M.D.		
Director, Clinical Affairs	Kathryn Kelley, R.N., B.S.N.		
Sr. Director, Quality & Regulatory	Naghmeh Nouri		
President/CEO	Scott Dodson		
Director, Research & Development	Mark Payne		

Statement of Agreement – Investigator

Protocol: CTP-0005

Study Title: Air**X**Panders **A**eroForm Tissue Expa**ND**er System for Breast Reconstruction (XPAND II)

Study Device: AeroForm® Tissue Expander System

IDE #: G110022

Protocol Version: 2.0

Study Sponsor: AirXpanders, Inc.

I have read this protocol and agree to participate in the clinical investigation of the AeroForm® Tissue Expander System sponsored by AirXpanders, Inc. I agree to conduct this investigation according to the requirements of the study protocol provided by the sponsor and in accordance with Good Clinical Practice guidelines and all applicable federal and state regulations as well as those conditions of approval imposed by the FDA and the governing Institutional Review Board.

I agree to supervise all use of the investigational device at my institution and to ensure that appropriate written informed consent is obtained from all subjects prior to the performance of any study procedure. I further agree to oversee all co-investigators and study personnel to whom I delegate responsibilities for the conduct of this study. I will provide copies of this protocol and all pertinent information to the study personnel under my supervision. I will discuss this material with them and ensure that they are properly trained regarding the use of this investigational device.

I understand that this investigation will be monitored by the Study Sponsor and/or a designee of the Study Sponsor. This monitoring will involve periodic inspection of my investigational site and ongoing review of the data that is submitted by me to the Study Sponsor.

My current curriculum vitae are on file with the Study Sponsor along the curriculum vitae of those Physicians at my institution who will be participating in this study as co-investigators under my supervision.

_____ _____

Principal Investigator Signature Date

_____Printed Name

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Protocol Synopsis

Protocol	CTP-0005, Version 2.0 IDE # G110022
Study Title	Air**XP**anders **A**eroForm Tissue Expa**ND**er System for Breast Reconstruction (**XPAND II**)
Sponsor	AirXpanders Inc.
Investigational Device	AeroForm® Tissue Expander System v2.5
Intended Use	The AeroForm Tissue Expander System is intended for use in post-mastectomy patients to develop tissue coverage prior to the placement of permanent breast implants. The device is intended for temporary subcutaneous or submuscular implantation and is not intended for use beyond six months.
Study Design	This is a prospective, multi-center, single arm, open-label, continued access clinical study. Subjects who meet the inclusion criteria and agree to participate in the study will be enrolled and implanted with the investigational AeroForm Tissue Expander. If the subject is having a bilateral procedure, the AeroForm expander will be implanted in each side. Subjects will be followed until the first post-operative visit after explant of the tissue expander(s) and exchange for permanent implant(s).
Study Objective	The objective of this study is to allow existing investigators continued access to the AeroForm Tissue Expander to treat patients while the company completes the marketing application and during the review process by FDA.
Primary Outcome Measure	The performance of the device will be evaluated by: Successful tissue expansion with exchange to a permanent breast implant unless exchange is precluded by a non-device related event. The primary endpoint will be analyzed per breast. Breasts in which the expander is removed and/or replaced due to a device related adverse event or a device malfunction will be counted as failures.
Secondary Outcome Measures	The safety of the device will be evaluated by: • Device related adverse events • All adverse events, regardless of whether serious or there is a causal relationship to the device. • Serious device related adverse events • All serious adverse events, regardless of whether there is a causal relationship to the device. • Device malfunctions leading to expander removal and/or replacement
Additional Outcome Measures	The usability of the device will be evaluated by: • The average number of days to achieve the desired expansion (onset of active expansion to completion of expansion) • The average number of days for completion of stage 1 reconstruction (expander implant to permanent implant). • Subject reported pain ratings at the onset of active expansion and one week after beginning active expansion

Protocol	CTP-0005, Version 2.0 IDE # G110022
Study Title	Air**XP**anders **A**eroForm Tissue Expa**ND**er System for Breast Reconstruction (**XPAND II**)
	• Overall subject satisfaction • Overall physician satisfaction • Reported device issues
Study Population	Women who are planning to undergo immediate or delayed breast reconstruction (unilateral or bilateral) post mastectomy and require tissue expansion to develop sufficient tissue coverage for placement of permanent implant(s). Up to 60 subjects will be enrolled in the study.
Investigational Sites	Up to 7 existing clinical sites will participate in the study. Investigators will be qualified board certified plastic and reconstructive surgeons with experience in breast reconstruction using tissue expanders and prior experience using the AeroForm Tissue Expander System.
Recruitment/Enrollment	Subjects will be recruited from current patient referrals at each site at the same rate of enrollment observed in the pivotal trial (XPAND). Investigators may enroll up to 4 subjects per month. The option of participating in the study will be discussed with the patients at their initial consultation visit and they will be given the informed consent. Once the patient has had adequate time to read the informed consent and have all of their questions answered, they will be asked if they would like to participate in the study. Once an informed consent is signed, patients will be enrolled in the study and scheduled for surgery.
Statistical Analysis Plan	This study is a continued access study and the results of this study will be analyzed in accordance with the statistical analysis plan for the XPAND study (CTP-0003).
Study Duration	Approximately one year
Subject Study Duration	Expected subject participation will be up to 6 months. Subjects will be followed from the time of implant to the first post-operative visit after explant of the tissue expander(s)
Inclusion Criteria	1. Subject is female between the ages of 18-70 2. Subject requires tissue expansion as part of breast reconstruction 3. Subject is able to provide written informed consent 4. Subject is able and willing to comply with all of the study requirements 5. Subject has the physical, perceptual and cognitive capacity to understand and manage the at home dosing regimen
Exclusion Criteria	1. Subject's tissue integrity is unsuitable for tissue expansion 2. Subject has residual gross malignancy at the intended expansion site 3. Subject has current or prior infection at the intended expansion site 4. Subject has a history of failed tissue expansion or breast reconstruction 5. Subject has any co-morbid condition determined by the Investigator to place the subject at an increased risk of complications (e.g., severe collagen vascular disease, poorly managed diabetes) 6. Subject is taking any concomitant medications determined by the Investigator to place the subject at an increased risk of complications (e.g., Prednisone, Coumadin).

Protocol	CTP-0005, Version 2.0 IDE # G110022
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	7. Subject is participating in a concurrent investigational drug or device study. 8. Subject is current tobacco smoker. 9. Subject is obese (BMI > 33). 10. Subject is unwilling to comply with instructions to notify the investigator and discontinue dosing prior to air travel, travel to a higher altitude and during the travel period. 11. Subject has an implanted electronic device such as a pacemaker, defibrillator, neurostimulator, or drug infusion device. 12. Subject is pregnant or planning on becoming pregnant during the study period. 13. Subject has a history of psychological condition, drug or alcohol misuse which may interfere with their ability to use the device safely.

1 Introduction

1.1 Background/Purpose

According the American Society of Plastic Surgery statistics, 95,589 women underwent breast reconstruction in the United States in 2013. The majority of women chose implant based reconstruction (76,278), with most performed as a two stage procedure using tissue expanders followed by permanent implants (68,607). The current standard of care tissue expanders are filled with saline via needle injection on a periodic basis until expansion is complete. Many women undergoing tissue expansion for breast reconstruction find this process uncomfortable and arduous requiring multiple office visits to complete the filling procedure. Physicians have long sought an alternative to the sterile procedure required to fill the current expanders.

AirXpanders, Inc., located in Palo Alto, CA, has developed a novel remote-control breast tissue expander (AeroForm Tissue Expander System) which is filled from an internal source with carbon dioxide (CO_2) eliminating the need for needle injections to fill the expander. This expander has the potential to make the process easier, faster and more comfortable while providing women with some degree of control over the expansion. The system is comprised of an implantable tissue expander which contains a reservoir filled with compressed carbon dioxide (CO_2), and an external hand held remote control. The controller activates the opening of an internal valve housed within the CO_2 reservoir to release carbon dioxide into the expander.

Enrollment in a prospective, multicenter, randomized, controlled clinical trial to evaluate the safety and effectiveness of the AeroForm tissue expander was completed in the U.S. in 2015. In this study, 150 women were randomized to either the investigational expander or saline expander control group using a 2:1 randomization design. Following mastectomy, subjects underwent a two stage procedure involving the placement of a tissue expander under the pectoralis major muscle and remaining skin of the absent breast. The expanders were placed either at the same time as the mastectomy (immediate reconstruction) or at some point after the mastectomy (delayed reconstruction) in unilateral or bilateral procedures.

Once adequate wound healing was confirmed, the expanders were gradually inflated using the remote control in the investigational group, and by periodic injections of saline in the control group. Once the overlying skin and muscle was stretched enough to provide adequate coverage, the expanders were removed and replaced by permanent breast implants.

This study is a continued access study designed for experienced investigators for the purpose of retaining their skills and experience with the device while the company completes a marketing application and during FDA review. The study is a single arm design with all subjects treated with AeroForm expanders.

1.2 Literature Review

The formal concept of surgical tissue expansion was first reported by Neumann in 1957, and further refined for breast reconstruction by Radovan and Argenta in the 1980s. Current standard of care using saline expanders requires months of weekly office visits for bolus injections and is associated with discomfort from high volume inflations, risk of infection and iatrogenic punctures of the expanders

A system designed for gradual, continuous expansion was shown by Bergé and others to be more rapid and well tolerated reducing the time burden and patient discomfort. In the Bergé study, investigators used an osmotic expander that continuously absorbed surrounding tissue fluid after deployment. However, a remaining concern was the inability to control osmotic expanders after they are deployed in the body.

Widgerow tested an expansion device using an external pump connected through tubing to the implanted expander which was controlled by the patient. He showed rapid time courses and patient satisfaction. However, the connector tubing imparted a cumbersome setup for the patient and the fear that prolonged connection to the external environment carries a high risk of contamination. Because the expanded pocket eventually receives a permanent implant, any level of contamination is unacceptable.

Reported complications from tissue expansion are typically due to poor tissue perfusion due to the poor vascularity of thin tissue flaps remaining following the

removal of breast tissue. The major complications involve wound healing issues with tissue necrosis, flap failure and infections which can lead to expander removal and failed reconstruction. Retrospective studies report an overall failure rate of 1.8 to 18%. Complications are exacerbated in this population in patients who undergo neo-adjuvant or adjuvant chemotherapy and radiation treatments for breast cancer.

Published reports published on the use of the AeroForm Tissue Expander System indicate that tissue expansion and breast reconstruction can be accomplished faster using this device with a similar complication rate to that reported in the literature (Connell, Ascherman, Zeidler). Connell and Zeidler also reported that radiation therapy can be delivered successfully with the expander in situ.

1.3 Pre-Clinical Testing

1.3.1 Bench Testing

The AeroForm Tissue Expander System has undergone thorough verification and validation testing that included:

- Biocompatibility
- Performance and functionality
- Stress and wear
- Sterilization validation
- Transit
- Shelf-life
- Electrical safety
- EMC
- Software validation

1.3.2 Animal Testing

A pre-clinical study was conducted in February 2009 using two sheep to confirm that the AeroForm Tissue Expander System operated as designed. Results of the *in vivo* sheep model study demonstrated that the device performed as intended (Jacobs). All implants consistently responded to user input via the hand-held remote control, desired volume expansion was achieved and no clinical safety-related issues were identified.

1.4 Human Clinical Testing (PACE I/II, XPAND, ASPIRE)

The first human feasibility study (PACE 1, Connell) was conducted at one investigational site in Perth, Australia beginning in June 2009. The study was a prospective, open-label, single arm feasibility study and established the safety of the AeroForm System for gradual, incremental breast tissue expansion prior to permanent breast reconstruction, paving the way for further clinical investigations.

Seven subjects were enrolled in the study and 10 AeroForm expanders (Clinical Version 1.0) were implanted in combination with a latissimus dorsi flap procedure. All seven subjects were successful using the device to complete their expansion at home and completed their reconstructions. The average length of active patient dosing was 15 days with a range of 5-22 days. The average time from expander implant to exchange for a permanent implant was 105 days with a range of 69-196 days. During the course of this study, some expanders had a higher than expected degree of permeation and required additional interim dosing. This permeation was traced to a design issue (molding seam) that was eliminated in Clinical Version 2.0.

Beginning in 2011, an additional 33 subjects were enrolled at the same site in the next phase of the study (PACE II, Connell). Sixty-one (61) AeroForm Tissue Expanders (Clinical Version 2.0) were implanted, and all 33 subjects successfully completed expansion and reconstruction. The average time to complete the expansion was 17 days and the average time to complete reconstruction was 90 days.

In a continued access study (ASPIRE) in Australia conducted in 2013 an additional 21 subjects were enrolled with 34 expanders implanted. The average time to complete the expansion was 22 days and the average time to complete reconstruction was 96 days. Two subjects in this study had prolonged courses due to complications related to poor tissue perfusion of dermal flaps that were used as an alternative to the investigators typical latissimus flap procedure.

In parallel to PACE II and ASPIRE, a prospective, multi-center, randomized, controlled clinical trial was initiated in the United States in October 2011 with enrollment completed in December 2014. A total of 150 subjects were treated after randomization (2:1 AeroForm to saline expander - 98 AeroForm, 52 Saline) at 17 sites with 168 AeroForm expanders and 89 saline expanders implanted. The

bilateral rate was 71%. The study was conducted with Clinical Version 2.0 (90 expanders) and Clinical Version 2.5 (78 expanders). Clinical version 2.5 was introduced during the trial to improve the barrier layer of the expander which contains the CO_2 and to allow the physicians increased access to the available CO_2 in the reservoir.

1.5 Marketing Authorizations

The AeroForm Tissue Expander has received CE marketing, but marketing and sales in Europe has not commenced. Additionally, a license approval has been granted by the TGA (Australia), and a limited market release of the product began in September, 2014. Limited data are available from the commercial experiences in Australia.

2 Study Rationale

The creation of a stable formed pocket for placement of a permanent implant is the foundation of successful implant based breast reconstruction, which can significantly improve the quality of life for a woman following the devastating effects of breast cancer.

The AeroForm System provides a needle free alternative to standard saline expanders and allows patients to participate in the expansion process with oversight by their physician. Tissue expansion with the AeroForm System eliminates the need for periodic bolus injections and may be performed at the patient's convenience at home under the direction of the physician. The incremental release of CO_2 on a daily basis allows a more gradual method of tissue expansion than with saline expanders.

Results of the previous clinical studies provides evidence that the AeroForm expander can be used safely and effectively to create the space needed to support permanent breast implants. Continued access to this technology is necessary to confirm the performance, collect additional usability data and refine best practices for its use.

3 Study Design

This is a prospective, multi-center, single arm, open-label, continued access study. Subjects who meet the inclusion criteria and agree to participate in the study will be

enrolled and implanted with the AeroForm Tissue Expander. If the subject is having a bilateral procedure, the investigational expander will be implanted in each side. Subjects will be followed until the first post-operative visit after explant of the tissue expander(s) and exchange to permanent implant(s). The study will be conducted according to IDE regulations.

4 Study Objectives

The objective of this study is to allow existing investigators continued access to the AeroForm Tissue Expander to treat patients while the company completes the marketing application and during the review process by FDA.

4.1 Primary Outcome Measure

The performance of the device will be evaluated by:

Successful tissue expansion with exchange to a permanent breast implant unless exchange is precluded by a non-device related event. The primary endpoint will be analyzed per breast. Breasts in which the expander is removed and/or replaced due to a device related adverse event or a device malfunction will be counted as failures.

4.2 Secondary Outcome Measures

The safety of the device will be evaluated by:

- Device related adverse events
- All adverse events, regardless of whether serious or there is a causal relationship to the device.
- Serious device related adverse events
- All serious adverse events, regardless of whether there is a causal relationship to the device.
- Device malfunctions leading to expander removal and/or replacement.

4.3 Additional Outcome Measures

The usability of the device will be evaluated by:

- The average number of days to achieve the desired expansion (onset of active expansion to completion of expansion)
- The average number of days for completion of stage 1 reconstruction (expander implant to permanent implant exchange).
- Subject reported pain ratings at the onset of expansion and one week after beginning active expansion
- Overall subject satisfaction
- Overall physician satisfaction
- Reported device issues

5 Statistical Considerations and Analysis Plan

5.1 Introduction

This is a prospective, multi-center, single arm, controlled, open-label continued access study. The results will be analyzed in accordance with the statistical analysis plan for the XPAND study (CTP-0003, v 9.0).

All subjects will be followed on an intent-to-treat basis. The primary risk benefit analysis for the device will be assessed based on a per protocol analysis of the primary performance and safety endpoints. Modified Intent-to-Treat and Safety analyses, along with other secondary analyses, will also be completed and reported.

6 Study Population

The study population will consist of women who are planning to undergo immediate or delayed breast reconstruction (unilateral or bilateral) post mastectomy and require tissue expansion to develop sufficient tissue coverage for placement of the permanent implant(s). Up to 60 subjects will be enrolled in the study.

7 Subject Enrollment

Subjects will be selected from current patient referrals at each site. Study participation will be open to subjects of all ethnicity and races. The demographics are expected to reflect those of the current population of patients undergoing reconstructive surgery. The option of participating in the study will be discussed with the patients at their initial consultation visit and they will be given the informed consent to take home and read. Once the patient has had adequate time to read the informed consent and have all of their questions answered, they will be asked if they would like to participate in the study. Once an informed consent is signed, patients will be enrolled in the study and scheduled for surgery.

7.1 Inclusion Criteria

1. Subject is female between the ages of 18-70
2. Subject requires tissue expansion as part of breast reconstruction
3. Subject is able to provide written informed consent
4. Subject is able and willing to comply with all of the study requirements
5. Subject has the physical, perceptual and cognitive capacity to understand and manage the at home dosing regimen

7.2 Exclusion Criteria

1. Subject's tissue integrity is unsuitable for tissue expansion
2. Subject has residual gross malignancy at the intended expansion site
3. Subject has current or prior infection at the intended expansion site
4. Subject has a history of failed tissue expansion or breast reconstruction
5. Subject has any co-morbid condition determined by the Investigator to place the subject at an increased risk of complications (e.g., severe collagen vascular disease, poorly managed diabetes)
6. Subject is taking any concomitant medications determined by the Investigator to place the subject at an increased risk of complications (e.g. Prednisone, Coumadin)
7. Subject is participating in a concurrent investigational drug or device study
8. Subject is current tobacco smoker
9. Subject is obese (BMI > 33)

10. Subject is unwilling to comply with instructions to notify the investigator and discontinue dosing prior to air travel, travel to a higher altitude and during the travel period.
11. Subject has an implanted electronic device such as a pacemaker, defibrillator, neurostimulator or drug infusion device.
12. Subject is pregnant or planning on becoming pregnant during the study period.
13. Subject has a history of psychological condition, drug or alcohol misuse which may interfere with their ability to use the device safely.

8 Study Duration

Subjects will be enrolled over a six month period. Total study duration is expected to be up to one year.

9 Subject Study Participation

Subject participation will be up to 6 months. Subjects will be followed from the time of implant to the first post-operative visit following explant of the expander (s) and exchange to permanent implant (s). It is expected that all subjects will have the expander(s) removed and permanent implant(s) placed within 6 months.

10 Subject Withdrawal

Participation in the XPAND II study is voluntary. A subject may withdraw their consent at any time during the course of the study. If the subject withdraws their consent prior to the expander implant procedure, the subject will be withdrawn from the study. If the subject desires to withdraw their consent following the implant, the risks associated with withdrawal from the study will be discussed with the subject. If the subject chooses to withdraw, the device must be explanted. The Investigator may withdraw a subject from the study prior to the implant procedure if he/she determines that the subject is not an appropriate candidate. Following implant, the Investigator should continue to follow the subject until the investigational device is explanted.

11 Study Visits

11.1 Pre-Screening

At the initial consult with the plastic reconstructive surgeon, women who are planning on having two-stage breast reconstruction will be asked to consider participating in the XPAND II clinical study. A standard HIPAA authorization will be placed in the medical record allowing access to their personal health information and pre-screening for eligibility may be done. Patients will be given the written informed consent to read at home. If after thoroughly reading the consent the patient is interested in study participation, a screening visit will be scheduled.

11.2 Screening/Enrollment/Pre-Operative Visit (Pre Implant)

Day (- 30) to Day (- 1) (Required)

The initial screening visit will occur between 1-30 days prior to the planned surgery date. This visit may be scheduled in conjunction with the standard pre-operative visit.

At the screening visit the following procedures/assessments will be performed:

HIPAA Authorization

The subject will be asked to sign a study specific HIPAA authorization form acknowledging their consent to allow access to their personal health information by study staff, designated sponsor staff and required regulatory authorities during the course of their study involvement.

Informed Consent

The IRB approved informed consent form will be reviewed with the subject after they have had adequate time to read the form in its entirety. The subject will be encouraged to ask questions and confirm their understanding of the study protocol and procedures. The informed consent form will be signed by the subject, the designated study personnel delegated to administer the informed consent process and the subject will be given a fully executed copy. No study procedures may be performed or data collected prior to the completion of the informed consent.

Inclusion/Exclusion Criteria

The inclusion and exclusion criteria will be reviewed with the subject. The subject may be enrolled in the study only if they meet all of the inclusion criteria and none of the exclusion criteria. If any of the inclusion criteria are not met or if any of the exclusion criteria are met, the subject will not be enrolled in the study and will be considered a screen failure.

Medical History

The subject will be interviewed by delegated site personnel and all pertinent medical and surgical history will be recorded on the history and physical form.

Physical Exam

A brief physical exam will be performed by qualified site personnel. Any abnormal findings will be recorded on the history and physical form.

Concomitant Medications

Prescription concomitant medications will be recorded at the screening visit. Any changes to the concomitant medications will be recorded at each study visit. Subject's will be asked to discontinue any medications such as blood thinners or platelet inhibitors (NSAIDs, Aspirin, Clopidogrel) that may place the subject at an increased risk of surgical complications prior to the operative procedure per the standard of care. It is not required to record vitamins, herbs, stool softeners, sleep medications or anesthetic agents given during the procedures.

Laboratory Tests

No study specific laboratory testing is required. Routine pre-operative laboratory testing will be done per standard of care. A urine pregnancy test will be performed at the screening visit for women of childbearing potential. If the test is positive, the subject cannot be enrolled in the study. Study subjects will be counseled to use a medically acceptable form of birth control during the study period.

Pre-operative Photographs

Photographs will be taken of the chest wall prior to surgery. The photographs will be taken in accordance with AirXpanders Photography Protocol.

Patient Teaching and Assessment

All subjects will be provided the Patient Teaching presentation on the AeroForm System and shown teaching models of the AeroForm Tissue Expander and the AeroForm Dosage Controller. The use of the dosage controller will be explained verbally and the patient will be given Patient Home Instructions to take home and review. The subject will be given adequate time to review the material and ask questions. The subject will verbally confirm their understanding, demonstrate their ability to operate the device and confirm their willingness to use the device for home tissue expansion. Note that patient teaching is an ongoing process and should be done at all visits.

Enrollment

The subject will be considered enrolled in the study once the written informed consent is signed, the inclusion/exclusion criteria have been confirmed and all screening procedures have been completed. A subject specific identifier will be assigned at that time. AirXpanders will be notified of patient enrollment and the scheduled implant date.

11.3 Operative Visit (Implant)

Day 0 (Required)

At the operative visit the following procedures/assessments will be performed:

- Confirmation of Inclusion/Exclusion Criteria
- Surgical Procedure (Expander Implant)
- Intraoperative Dosing
- Device Accountability
- Operative Report (copy to subject study file)
- Physician Device Evaluation
- Concomitant Medications
- Adverse Events

- Patient Teaching
- Subject will be given the Patient ID Card with emergency contact information prior to discharge

11.4 Post-Operative Follow Up Visits (Post Implant)

Day 7 +/- 3 days, Day 14 +/- 3 days, Day 21 (+/- 3 days) then every two weeks (+/- 5 days) until expansion is started.(Required)

After surgery, tissue perfusion and wound healing status will be assessed to determine readiness for active home expansion. Once the subject is ready to begin active home expansion, she will be given the dosage controller (s) and instructed on daily dosing. The Patient Home Instructions will be reviewed with the subject prior to starting home expansion.

At the post-operative visits the following procedures/assessments will be performed:

- Surgical Site Assessment
- Concomitant Medications
- Adverse Events
- Patient Teaching
- MD Dosing (Optional)
- Record Date Home Expansion is Started (start of home dosing is at the discretion of the investigator based on wound healing and subject comfort)
- Photographs (on the day that home expansion is started). Photographs should also be taken to document any adverse events related to the breast.
- Numeric Pain Scale (A standard 11 point numeric pain scale will be completed by the subjects on the day that home expansion is started)

11.5 Expansion Follow Up Visits (During Home Expansion)

1 week post home expansion start date (+/- 3), then every two weeks (+/-5) until expansion is complete, then monthly until the exchange procedure.

After home expansion begins, subjects will be assessed for expansion progress. Once full expansion is reached, subjects will be instructed to dose once or twice per week to maintain the volume and visits may then occur monthly. Once the

subject is ready for exchange, the procedure will be scheduled and AirXpanders will be notified of the scheduled explant date.

At the expansion follow up visits the following procedures/assessments will be performed:

- Surgical Site Assessment
- Expansion Assessment
- Numeric Pain Scale (A standard 11 point numeric pain scale will be completed by the subjects one week after the start of home expansion, and on the day expansion is complete)
- Photographs (on the day that expansion is complete). Photographs should also be taken to document any adverse events related to the breast.
- Concomitant Medications
- Adverse Events
- MD Dosing (Optional)
- Record Date Expansion is Complete (subjects to discontinue daily dosing and begin maintenance dosing at least once per week until explant)
- Patient Teaching

11.6 Operative Visit (Explant/Exchange to Permanent Implant)

Investigators Discretion (Not > 6 months post implant)

The investigator will determine when the subject is ready to exchange to permanent implants. The expander(s) will be explanted and returned to AirXpanders for evaluation. Second stage breast reconstruction will be completed with placement of permanent implant(s).

At the operative visit the following procedures/assessments will be performed:

- Tissue Expander Explant/Implant of Permanent Breast Prosthesis
- Device Accountability
- Operative Report (copy to subject study file)
- Concomitant Medications
- Adverse Events
- Physician Device Evaluation

11.7 Post-Operative (Post-Explant) Visit

1-2 week post-operative (explant)

Following the explant/exchange surgery the subject will be assessed and final reconstruction results documented.

At the post-operative visit the following procedures/assessments will be performed:

- Surgical Site Assessment
- Concomitant Medications
- Adverse Events
- Photographs (Photographs of the final reconstruction results will be taken)
- Subject Satisfaction Survey
- Physician Satisfaction Survey

11.8 Optional Visits/Additional Procedures

Optional visits may be scheduled at the discretion of the investigator i.e., for follow up of adverse events or evaluation of expansion progress. Any additional procedures performed during the course of the study such as needle aspirations, surgeries or radiation treatments will be recorded.

12 Device Description/Intended Use

12.1 Device Description

The AeroForm Tissue Expander System (Figure 1) is comprised of the AeroForm Tissue Expander, the AeroForm Dosage Controller and AeroForm Physician Master Key. For a full description and details of the components, please refer to the Instructions For Use (IFU).

12.1.1 AeroForm™ Tissue Expander (Implant)

The AeroForm Tissue Expander is a sterile product and consists of a textured outer shell, an inner CO_2 gas barrier, a stainless steel CO_2 reservoir and antenna/electronics for communication. The CO_2 reservoir has an internal valve

that is activated by the remote control to release a small, 10cc dose of CO_2. The release of CO_2 results in gradual expansion of the implant.

Following expansion, the expander is removed and exchanged for a permanent breast implant.

Figure 1: AeroForm Tissue Expander System

Table 1 lists the size options and corresponding model numbers for the AeroForm Tissue Expander. All models have a textured surface and anatomical shape.

Table 1 Available AeroForm Tissue Expander Models (Clinical Version 2.5)

Model #	Size	Width (cm) Un-inflated	Height (cm)	Projection (cm) Inflated	Volume (cc)
LP105-400	Small	12.5	11.0	8.0	400
LP120-650	Medium	14.0	12.5	9.5	600
LP130-850	Large	15.5	14.0	10.5	800

12.1.2 AeroForm Dosage Controller

The AeroForm Dosage Controller (Figure 2) is a small, battery operated, hand held controller that remotely activates the expander to release CO_2. The controller is configured to provide temporary power and coded instructions to the paired expander. It has a center button with a row of indicator lights and audible tones to provide position and CO_2 delivery information to the user. The controller is permanently bonded to an expander at the time of implant and will not function with

other expanders. The controller is programmed to deliver a dose of 10cc with each push of the button with a lockout period of 3 hours and a daily maximum of 30cc.

The controller tracks the timing and volume of dosing and estimates the volume of CO_2 in the expander. Once the controller estimates that the expander is at full volume, it is programmed to allow patient dosing in the amount required to maintain the labeled volume.

12.1.3 AeroForm Physician Master Key

The AeroForm Physician Master Key is used by trained medical personnel only. When the key is inserted into the controller, consecutive doses can be given with no daily limit on the interval between doses or the number of doses (up to the labeled volume of the expander). The physician may provide volume above the programmed limits if needed using *Physician Fill Mode*. Dosing beyond the labeled volume should only be done if there is a loss of volume.

The Physician Master Key allows trained medical personnel to:

- Test the AeroForm expander in the operating room prior to implant
- Fill the expander to the desired intra-operative volume
- Add volume to the expander during office visits
- Add volume to the expander after labeled volume has been reached, if needed, due to a loss of volume

The key is to be retained by the physician for their use only and is not to be provided to the subjects. Figure 2 shows the controller and the key.

Figure 2: AeroForm Dosage Controller and AeroForm Physician Master Key

12.1.4 Accessories

An Aseptic Transfer Pouch is provided with the Dosage Controller for use during the implant procedure to maintain the sterile field.

12.2 Dosing

A dose is defined as the amount of CO_2 released within the expander each time the center button is pressed. The controller is programmed to limit a single dose to 10cc. The subject will not be able to administer a dose more than once every three hours with a maximum of 30cc in a 24 hour period. However, the surgeon may add volume if needed with the use of the Physician Master Key.

Prior to implant, the expander is bonded to a controller by inserting the Physician Master Key that is packaged with the expander into the slot on the bottom of the controller. A test dose is administered prior to implant to confirm that the controller is communicating with the expander. Following implant, an initial series of 10cc doses are administered to fill the surgical pocket. Post-operative, once the surgical site is adequately healed and the patient is comfortable, the first daily dose is administered in the physician's office. The subject is then instructed to administer daily doses (10cc) up to three times daily, dependent on their comfort level. At

expansion follow up visits, the physician may administer additional doses in the office based on subject and tissue tolerance using the Physician Master Key. Once full expansion has been achieved, the patient should be instructed to administer weekly doses until explant to maintain the volume of the expander.

12.2.1 Physician Fill Mode

When the AeroForm expander reaches the programmed volume, the indicator lights will flash and the controller will shut off. If the Physician Master Key is inserted and the controller is turned back on, the programming converts to Physician Fill Mode which allows the physician to administer up to 25% of the labeled volume every two weeks.

This mode is intended to be used only when the physician assesses that the expander needs additional fill to maintain full volume.

Dosing above the labeled volume may result in an increase in the relative pressure of the expander. Expander fill should be assessed by the physician based on tissue laxity, perfusion and firmness of the expander. Care should be taken to ensure that overfilling does not occur.

Once the controller has converted to Physician Fill Mode, no patient dosing will be possible, therefore, the controller will have no functional value to the patient and may be kept by the physician. Any further dosing will need to be done in the office.

12.3 Intended Use

Tissue expanders are intended for single patient use in post-mastectomy patients to develop adequate tissue coverage for the placement of permanent breast implants. The AeroForm expander is intended for temporary subcutaneous or submuscular implantation and is not intended for use beyond six months.

12.4 Protocol/Device Training

Training will be provided by the Sponsor to the Principal Investigator (PI), Co-Investigators, and site study staff at the site initiation visit. The training will include, at a minimum, the protocol requirements, device training, implant and explant procedures specific to the device, post-operative follow up, dosing, device

accountability, contraindications, warnings and precautions as stated in the Instructions For Use.

The study staff will in turn, train the subjects on the protocol requirements, device function, dosing considerations, dosing limits, dosing steps, contraindications, warnings and precautions. Written material will be provided to train the subjects on the AeroForm System and Patient Home Instructions will be provided.

12.5 Device Accountability

This AeroForm System is labeled for investigational use only in the United States. The investigator is responsible for ensuring that it is used only in subjects enrolled in the study as well as for maintaining accountability of all investigational devices in their possession. Each expander is supplied with multiple patient record labels showing the model number and lot number for that expander. One of these labels should be attached directly to the subject's chart. A second label should be attached to the bonded controller. Additional labels are provided to be used, as needed.

12.6 Device Disposition

The Investigator shall maintain records of the receipt and disposition of all investigational devices. When enrollment is complete, the Investigator shall return any unused devices to the sponsor. At the time of explant, the controller is to be returned to AirXpanders. The explanted tissue expander should be returned to AirXpanders with the appropriate biohazard packaging supplied by the sponsor.

12.7 Device Malfunction/Damage/Loss

All device malfunctions should be reported to the Sponsor immediately and recorded on the device malfunction CRF. If an expander malfunctions, explant and replacement may be necessary. In the event of an expander malfunction requiring replacement, investigator and subject will have the option of replacement with the investigational expander or a standard saline expander.

Dosage Controllers are intended for single patient use. One controller will be bonded with one expander at the time of implant. Subjects with bilateral implants will have two controllers, one for each expander. The controllers will be labeled to indicate which expander/side it is bonded to. The implanted expander can only be

activated by the bonded controller. Subjects with bilateral expanders should be instructed to dose one implant at a time. If a controller is lost or damaged a replacement controller will be provided and bonded with the respective expander.

13 Benefits/Risks

The device has the potential to make the expansion process faster, more comfortable and more convenient for both the patient and physician.

13.1 Benefits

Tissue expansion with saline tissue expanders is a lengthy and uncomfortable experience. The AeroForm System is designed to allow for non-invasive, incremental expansion which can be controlled by the patient. Tissue expansion with the AeroForm System eliminates the need for weekly injections of saline and may be performed at the patient's convenience at home under the direction of their physician. Incremental dosing on a daily basis provides a gradual method of expansion that can be adjusted according to a patient's pain level, thus providing an easier, more comfortable method of expansion. Results of the previous clinical studies indicate that the AeroForm System is safe and effective for breast tissue expansion and can expedite the expansion and reconstruction process.

13.2 Clinical Risk Analysis

Most risks associated with the use of the AeroForm System are similar to those associated with saline-filled tissue expanders. Undergoing any surgical procedure may involve the risk of complications from the effects of anesthesia or the surgical procedure. There are common side effects that may occur with any tissue expander implant such as inflammation, bruising, bleeding, hematoma, seroma, fever, infection, pain, paresthesia, scarring, stretch marks, skin breakdown, wound dehiscence, skin necrosis, extrusion, capsular contracture, chest wall deformity, displacement, or allergic reactions.

There are also device malfunctions that may occur with either type of expander such failure to expand or deflation due to internal causes (valve failure) or due to external causes such as implant leak or inadvertent needle puncture. Implant

rupture can occur from over-pressurization of the implant or from blunt force trauma. If failure to expand, deflation, leaking, needle puncture, or rupture occurs, device removal and/or replacement will be necessary.

13.2.1 Device Malfunctions

13.2.1.1 Failure to Expand or Deflation

The expander will not be able to be fully inflated if:

- The expander antenna does not respond to the controller
- The controller fails to operate properly
- The valve of the CO_2 reservoir fails to open
- The valve does not release the correct amount of CO_2
- There is not enough CO_2 in the reservoir to achieve final volume
- There is a leak in the implant or excessive permeation through the CO_2 barrier

If the expander fails to expand or becomes deflated, removal and/or replacement may be necessary.

13.2.1.2 Over Expansion and/or Rupture

Over expansion of the expander may occur if:

- There is a change in altitude greater than approximately 3300 feet (1000 meters) from baseline leading to CO_2 expansion
- The expander is filled beyond the tissue tolerance or patient comfort due to a device malfunction or operator error
- The valve fails and leaks or is stuck in the open position leading to a slow or rapid release of CO_2

Rupture of the expander may occur if:

- The volume of the inner gas barrier increases beyond the maximum labelled volume
- The expander is damaged either by a sharp instrument or by blunt force trauma

An increase in volume could lead to pain and/or wound dehiscence (dependent on the healing stage of the surgical site). Once the labeled volume is reached, the

pressure inside the non-distensible inner gas barrier will increase if additional volume is added up to the point at which the gas barrier will rupture. The rupture will typically present as an opening in the anterior wall of the gas barrier through which CO_2 will be released into the space between the inner barrier and outer silicone shell. The gas will permeate through the ventilation holes and the porous outer shell and dissipate in the surgical pocket (subcutaneous/subpectoral space) and surrounding tissue likely resulting in temporary subcutaneous emphysema. The CO_2 will be absorbed by the body via diffusion from the tissue into the bloodstream and eliminated through normal gas exchange in the lungs. If wound dehiscence occurs, CO_2 will be released via the separation of the wound. If necessary, the expander may be deflated with a hypodermic needle. The device may require removal and/or replacement (depending on the stage of expansion).

13.2.2 Unknown Risks

As with any investigational device, there may be risks associated with the use of the AeroForm System that are unknown. Any unexpected adverse device effect should be reported to the sponsor immediately.

13.2.3 Mitigations

AirXpanders has designed, manufactured and thoroughly tested the AeroForm System to minimize the potential complications associated with its use. This study protocol has been designed to protect the safety of the participants.

A thorough biocompatibility study was performed on all materials used in the implant that are, or could come into patient contact. Additionally AirXpanders corporate quality control systems enforce that no unintended materials are used in the manufacture of the device.

13.2.3.1 Mitigations to prevent under expansion

The electronics and communication between the reservoir valve and the controller have been tested extensively as part of the quality assurance process, as well as during bench, animal and human studies. A replacement dosage controller can be provided and bonded with the implant if the expander stops communicating with the dosage controller or the dosage controller fails to operate. The CO_2 reservoir valve had been tested extensively and the reservoir is filled with a sufficient

amount of compressed CO_2 to inflate the tissue expander to the labelled volume and account for expected loss due to permeation. The inner gas barrier of the expander was specifically designed to minimize the loss of CO_2. The seals of the expander have been reinforced and tested to minimize the chance of leaks.

Once the desired volume is reached, if more than expected loss of volume occurs, intermittent dosing (up to 25% of the labelled volume every two weeks) using Physician Fill Mode can be done to maintain the volume of the expander.

13.2.3.2 Mitigations to prevent over expansion

Once the CO_2 is released into the implant, it may expand if there is a significant change in altitude. This is due to the fact that CO_2 expands at higher altitudes such as during air travel. The instructions for use and device labelling contain warnings and precautions for patients planning air and mountain travel. Subjects will be required to inform their physician prior to travel and discontinue dosing for a period of at least two weeks prior to travel until their return. Care should be taken not to over fill the expander beyond tissue tolerance or patient comfort since there is no way to remove CO_2.

The possibility of over filling the expander is reduced through the programmed limits of a maximum daily dose of 30cc and the interval lock out period of 3 hours. Only the investigator may add volume above these limits with the use of the Physician Master Key. The limits are intended as a patient safety feature only and are not meant to be prescriptive. The physician should exercise his/her clinical judgement to fill the expander to the desired volume according to tissue tolerance and subject comfort as noted in the Instructions For Use (IFU).

The AeroForm System has been designed and tested to address potential failures of the device that may lead to over expansion. The reservoir valve is manufactured with a non-reactive material and has been designed to fail in the closed position, thus minimizing the risk of over expansion.

13.2.3.3 Mitigations to prevent device rupture

As noted above, the AeroForm System has been designed to mitigate against over-expansion which may lead to excessive pressure and potential device

rupture. Labeling and training are in place to take precautions when traveling to higher altitudes or over-filling the expander. The valve is designed to fail in the closed position minimizing the possibility of a rapid release of CO_2. Injury by blunt trauma or sharp objects may result in damage to the expander, resulting in rupture which may occur with any implant. In the event of a sudden rupture of the AeroForm expander, an accumulation of CO_2 under the skin (subcutaneous emphysema) could occur. CO_2 is a natural product of cellular activity and is highly soluble in tissue and was chosen specifically because of its demonstrated safety when used in the body for other medical purposes. Any risks associated with tissue contact with the CO_2 and the inner components of the device are negligible as both are composed of common materials used for medical purposes and are sterilized.

Rupture of the device will disable the device and will require immediate medical attention and removal of the expander.

13.2.4 Protection of Study Subjects

AirXpanders has incorporated several procedures into the investigational plan and system labelling to protect study patients from any potential adverse device effects. There are stringent inclusion/exclusion criteria in the investigational protocol that will exclude any study subject who may be at increased risk of complications. The investigational protocol requires routine office visits to assure that any acute adverse effects are detected in a timely manner and proper medical treatment can be initiated. Subjects will be instructed to call their doctor immediately if they encounter any problems with the device or experience signs of complications. The Instructions for Use (IFU) describes the proper technique for the implantation procedure and expansion process in detail and training will be provided to both Investigators and study subjects on the proper use of the device. Device Training, Investigator and Patient Reference Cards along with Patient Home Instructions are provided to reinforce this training. Only Investigators who are experienced and skilled in using breast tissue expansion devices for breast reconstruction and who are trained to the protocol and the AeroForm Tissue Expander System will be selected for participation in the study.

13.2.5 Human Factors Considerations

AirXpanders has designed this device with consideration of human factors to minimize misuse of this device. Features incorporated into the device include software controls such as limiting the dosing to 10cc, 3 hour lock out intervals for repeat dosing and a maximum daily dose of three doses or 30cc. A Physician Master Key is required to dose beyond the pre-set maximum dose and dosing intervals. Labeling mitigations include Instructions for Use (IFU), Physician and Patient Reference Cards and Patient Home Instructions. Physician and patient training materials are provided prior to use of the device. Subjects will be given a Patient ID card with information for 24 hour emergency contact in the event of any device problems.

13.2.6 Contraindications

The AeroForm Tissue Expander is contraindicated when:

- Tissue at the intended expansion site is determined unsuitable by the physician. To a varying degree, radiation damage, ulceration, compromised vascularity, history of compromised wound healing, infection or scar deformity may affect tissue suitability.
- There is residual gross tumor at the intended expansion site.
- There is a pre-existing physiological condition, determined by the physician, which pose a high risk of surgical or postoperative complications. To a varying degree, sensitive overlying or underlying anatomy, obesity, smoking, diabetes, autoimmune disease, hypertension, chronic lung or severe cardiovascular disease, or osteogenesis imperfecta may affect patient suitability for surgery.
- The patient has another electronic implant (e.g., pacemaker, defibrillator, or neurostimulator device)

13.2.7 Warnings

Radiation Therapy

Functional testing of the AeroForm Tissue Expander at radiation levels exceeding standard clinical practice has been performed, demonstrating no degradation in functionality. However, AirXpanders does not provide recommendations regarding the use of radiation therapy. As with any implant, the decision to use radiation

therapy should be made with the consultation of the radiation oncologist using standard radiation treatment planning.

If radiation therapy is planned, the risks of radiation therapy and alternative treatment options should be discussed with the patient. In the event that radiation therapy is administered, there should be no active expansion during radiation therapy.

Overfilling

The reservoir inside the AeroForm Tissue Expander releases a controlled amount of CO_2 when the button on the hand-held controller is activated. AirXpanders recommends that the physician and the patient expand gradually. Expansion progress should be assessed by the physician based on tissue laxity, perfusion and firmness of the expander.

Note that the AeroForm Tissue Expander has a non-distensible inner liner which cannot be inflated beyond the labeled volume. Dosing beyond the labeled volume or too rapid tissue expansion may lead to increases in the relative expander pressures, possibly leading to discomfort, wound dehiscence, tissue damage or rupture of the expander. If that occurs, stop expansion immediately.

Altitude Change

Patients with an implanted tissue expander considering travel to a higher altitude should consult with their physician prior to their travel. They should be instructed to discontinue dosing for at least two weeks prior to their travel and resume dosing after their travel is complete.

An increase in altitude will lead to an increase in the expander volume and the relative internal pressure, which may cause discomfort, wound dehiscence, or damage to the expander. The volume increase will be reversed upon descent.

MRI

Do not undergo diagnostic testing with Magnetic Resonance Imaging (MRI) with the AeroForm Tissue Expander in place. MRI equipment can cause movement of the expander and result in patient injury, or expander displacement requiring revision surgery. In addition, the metal CO_2 reservoir could interfere with MRI detection capabilities.

Infection

Patients who present with any active infection may need to be treated and the infection resolved before placement of the expander. Do not expose the expander to contaminants that could increase the risk of infection. Patients who present with active infection, wound dehiscence, tissue erosion, ischemia, or necrosis run an increased risk of periprosthetic infection.

Temporary Device

The AeroForm Tissue Expander is a temporary device intended for up to six months of implantation, and is not to be used for permanent implantation. Expanders should be removed once adequate tissue has developed. The total expansion period will vary depending on patient tolerance, tissue tolerance, and planned permanent implant size.

13.2.8 Precautions

Surgical Planning

The physician should follow proper surgical procedures to minimize the occurrence of adverse reactions. A qualified physician must carefully evaluate patient suitability for expansion and desired physical outcome, expander dimensions, incision placement, pocket dissection, expander filling, and final flap dimensions using current, accepted techniques and individual experience.

Contamination at Surgery

To avoid contamination, aseptic technique is essential. Do not expose the expander to lint, talc, sponge, towel, and other contaminants. Contamination at the time of surgery increases the risk of periprosthetic infection which could require premature explantation of the expander.

Damage During Surgery

Take extreme care to avoid damage to the expander during surgery; for example:

- Excessive manipulation by forcing the expander through too small an access incision or into a small surgical pocket.

- Sharp surgical instruments, such as scalpels and needles used during the initial surgery, or hematoma/fluid evacuation. During surgery, have a sterile back-up expander readily available in case damage occurs. Products must be carefully inspected for leaks or nicks prior to use. Do not attempt to repair damaged products.

Hemostasis and Avoiding Fluid Accumulation

Minimize post-operative hematoma and seroma by meticulous attention to hemostasis during surgery, and possibly by postoperative use of closed drains.

Persistent, excessive bleeding must be controlled before the expander is placed. The expander may be filled to tissue tolerance at the time of surgery to help minimize serous fluid accumulation in the surrounding pocket. Any postoperative evacuation of hematoma or other fluid accumulation must be carefully conducted to avoid introduction of contaminants or damage to the expander from needles or other sharp instruments.

Physician Expansion

- DO NOT over inflate the expander, as there is no method to remove volume. For patient safety, the expander has a default maximum dose of 30cc per day. However, actual volume delivery should be guided by patient comfort and wound status.

- Excessive pressure from over expansion can lead to discomfort, wound dehiscence, tissue damage or rupture of the expander. In an emergency, the device can be deflated with a standard hypodermic needle.

- DO NOT give the Physician Master Key to the patient at any time. It is to be used exclusively by the physician to administer doses during patient office visits when therapeutically appropriate.

- If the patient has bilateral implanted expanders, she should be instructed to expand one at a time, using the controller labeled for that expander. She should not attempt to expand both expanders simultaneously using both controllers.

- During dosing, if the expander appears to be filling excessively with accompanying patient pain and/or discomfort, remove the controller from the proximity of the expander. Contact AirXpanders for technical support.

Electromagnetic Interference

The ability to establish communication between the AeroForm Tissue Expander and the Dosage Controller may be impaired by electromagnetic interference from other RF wireless devices operating nearby. Interference from other RF wireless devices may be resolved by simply moving away from the other RF wireless device.

Subjects who work in areas of high radiation, magnetic or electrical fields should discuss this with their physician prior to implantation.

Over-expansion/Rupture

- Over-expansion of the expander due to device malfunction or excessive filling by the physician, can lead to extreme pain and/or wound dehiscence or may compromise the tissue integrity and require device deflation. If the subject experiences severe discomfort due to over inflation, the tissue integrity should be assessed and the subject should be treated as necessary. The expander can be deflated with a small gauge needle however; this will permanently disable the expander necessitating removal.

- The expander could rupture if the pressure inside becomes excessive due to over expansion, a rapid release of CO_2 into the expander, a significant change in altitude, or sharp or blunt force injury to the chest. Damaged, leaking, or broken expanders cannot be repaired and may require replacement surgery.

No-expansion/Under-expansion

- Under-expansion of the expander due to device malfunction or excessive permeation of CO_2 through the inner liner could occur. Advise patients that the expanders may deflate, and require replacement surgery.

13.2.9 Other Considerations

Chemotherapy

During the course of the study, some subjects may have to undergo adjuvant chemotherapy treatment. This may delay the explant of the expander to allow for the immune system to recover prior to surgery. In the event of a delayed exchange due to chemotherapy, the subject should continue to be followed per the study protocol. If the subject is unable to maintain the study schedule due to chemotherapy, this should be documented and the sponsor should be notified.

14 Adverse Events

During the course of the study, adverse event data will be collected according to the definitions below:

14.1 Adverse Event (AE)

An adverse event is defined as any untoward medical occurrence in a subject, regardless of whether the event is related to the device. All adverse events occurring during the subject's participation from the time of implant to the time of explant of the expander(s) will be recorded on the AE Case Report Form. Data collected will include a description of the event, onset date, management or treatment/intervention required, outcome, and resolution date (or whether the AE is ongoing). Subjects with adverse events that are ongoing should be followed until resolution of a serious AE and/or if they may be device related. All AEs will be reviewed and assessed by the investigator for severity (Table 2) and causal relationship to the device (Table 3). The investigator will also determine whether the AE meets the definition of serious as described in Section 14.2.

The investigator will use the following definitions to rate the severity of each AE:

Table 2 Adverse Event Severity Rating

Severity	Description
Mild	• Awareness of a sign or symptom that does not interfere with the subject's usual activity or is transient, resolved without treatment **and** • no sequelae
Moderate	• Interferes with the subject's usual activity **and/or** • requires symptomatic treatment
Severe	• Symptom(s) causing severe discomfort **and** • significant impact on the subject's usual activity **and** • requires treatment

Note: Adverse events that are rated as severe are not the same as serious adverse events. For example a subject may have severe pain may require treatment but not lead to a 'serious' event as defined below.

14.2 Serious Adverse Event (SAE)

Any untoward medical occurrence in a subject, regardless of whether the event is related to the device that:

a. results in death;
b. results in a life threatening illness or injury;
c. results in a permanent impairment of a body structure or body function;
d. requires in-patient hospitalization or prolongation of existing hospitalization
e. results in medical or surgical intervention to prevent permanent impairment to body structure or function;
f. results in fetal distress, fetal death, or a congenital abnormality/birth defect.

14.3 Device Related Adverse Event

Any sign, symptom, or disease in a study subject that occurs during the course of a clinical study that is determined by the investigator to have a causal relationship or possible causal relationship with the investigational device.

Table 3 Adverse Event Device Relationship

Relationship	Description
Not Related	• Not associated with the device • due to an underlying or concurrent illness or effect of another device or drug
Unlikely	• Little or no temporal relationship to the study device **and/or** • a more likely alternative etiology exists
Possible	• Temporal sequence between device application and event is such that the relationship is not unlikely **or** • subject's condition or concomitant therapy could have caused the AE
Probable	• Temporal sequence is relevant **or** • Event abates upon device removal **or** • event cannot be reasonable explained by the subject's condition
Highly Probable	• temporal sequence is relevant and • event abates upon device removal **or** • reappearance of the event on repeat device application

14.4 Serious Device Related Adverse Event

Any sign, symptom, or disease in a study subject that occurs during the course of a clinical study that is determined by the investigator to have a causal relationship or possible causal relationship with the investigational device and meets the definition of serious as described above.

14.5 Unanticipated Adverse Device Event (UADE)

Any serious adverse effect on health and 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.

As with any investigational device, there may be risks associated with the use of the AeroForm System that are unknown. If any serious unanticipated device related adverse events occur during this study, they will be immediately (24 hours from knowledge of event) reported to the IRB and Sponsor in accordance with applicable regulations.

The following table summarizes the potential adverse events in this study:

Table 4 Adverse Events

Event	Definitions/Criteria
Surgical Site Inflammation	Severe erythema (redness), edema (swelling), and tenderness at the surgical site.
Bruising	Severe bruising (purple discoloration) at the surgical site
Bleeding	Significant bleeding at the surgical site requiring medical intervention or return to the operating room.
Hematoma	Collection of blood under the skin at the surgical site requiring medical intervention or return to the operating room for evacuation
Seroma	Collection of serous fluid under the skin at the surgical site requiring medical intervention or return to the operating room for drainage.
Fever	Post-operative fever of > 38.5◦ C (101.3◦ F)
Surgical Site Infection	Infection at the surgical site requiring medical treatment
Systemic Infection or Sepsis	Positive blood cultures and clinical diagnosis of sepsis
Pain	Severe pain requiring additional medical intervention or follow up
Sensory Loss	Significant numbness (paresthesia) at the surgical site
Tissue damage	Tissue thinning, necrosis, sloughing, (due to due to poor vascularization)
Wound dehiscence	Open wound at the expansion site
Extrusion	Extrusion at intended pressure, not wrinkle edge
Erosion	Exposure of the implant despite a lack of excessive pressure
Capsular contracture	Contracture of the pocket preventing adequate expansion
Malposition	Displacement of the implant due to migration
Reoperation	Any unplanned return to the operating room including device removal and/or replacement.
Other	Any other new sign or symptom that is reported by the subject during their enrollment in the study. Record by body system/event, i.e., Cardiac/Chest Pain, Pulmonary/Pneumonia that in the opinion of the investigator constitutes an adverse event.

14.6 Reporting of Adverse Events

For the purposes of this study, adverse events will be categorized based on their relationship to the device. The Investigator at each site is responsible for monitoring the safety of the subjects enrolled at that site and for determination of the causal relationship of all adverse events to the device. All adverse events determined by the investigator to be unanticipated, serious and/or possibly, probably or highly probably related to the device must be reported to the sponsor within 24 hours after the investigator first learns of the event and to the reviewing IRB per their written policy.

An investigator shall submit to the sponsor and to the reviewing IRB a report of any unanticipated non-serious adverse device event occurring during the investigation as soon as possible, but in no event later than 10 working days after the investigator first learns of the effect.

The Sponsor is responsible for the ongoing safety evaluation of the investigational product. The Sponsor shall be responsible for immediate adjudication of all reported serious and/or device related adverse events to determine whether the event is reportable under federal regulations. The sponsor will select a safety committee comprised of at least one physician who is neither an investigator in the study or employed by the sponsor to adjudicate all adverse events to determine if the event is related to the investigational device.

The Sponsor will promptly, within 10 working days after the sponsor first receives notice of the effect, notify all participating investigators and regulatory authorities, as appropriate, of findings that could affect adversely the safety of subjects, impact the conduct of the study or alter the IRB's approval opinion to continue the study.

If the Sponsor determines that an unanticipated adverse device effect presents an unreasonable risk to subjects, the Sponsor shall terminate all investigations or parts of investigations presenting that risk as soon as possible.

14.7 Additional Procedures, Pre-mature Explant, Device Replacement

As with any surgical procedure, additional procedures may be required in the event of an adverse event. The occurrence of complications may result in premature explant and/or replacement. Device replacement may be required if desired

volume is not achieved or if over-expansion leads to complications. Excess pressure may cause pain, ischemia, tissue injury or dehiscence of the wound if the pressure is not relieved.

14.8 Device Failures

Device Failures are defined as a malfunction of the device which leads device removal and/or replacement. Device malfunctions that occur but do not lead to an adverse event or removal and/or replacement will be reported as malfunctions but not be counted as failures. The table below lists potential device malfunctions. In the event of an adverse event requiring replacement of the AeroForm expander, this will be considered a treatment failure and the patient and surgeon will have the option of replacing the AeroForm with a replacement AeroForm expander or a standard saline expander.

Table 5 Potential AeroForm Device Failures

Event	Potential Causes
Failure to Expand	Leaking implant or Excessive Permeation leading to loss of CO_2 volume
	Inadequate CO_2 in the reservoir to achieve final volume
	Electronic Failure: Non-response of the reservoir valve to signal from hand held controller
	Valve Failure – Stuck in closed position
Device Deflation	Loss of CO_2 sufficient to cause complete deflation of the expander without adequate tissue expansion
Over-expansion	Increased volume as a result of significant altitude change
	Inadvertent overdose due to operator error
	Valve Failure – Failure to close or seal or stuck in open position
Device rupture	Sudden deflation of the expander due to device damage (puncture or blunt force trauma) or excessive pressure

15 Investigator and Site Qualification

Investigator sites will be selected per established AirXpanders standard operating procedure to ensure that Investigators and research staff are qualified with appropriate training and experience to investigate the device. At a minimum, Investigators will be qualified to practice, board certified and experienced in the field

of breast reconstructive surgery using tissue expanders. Investigators with previous experience using the AeroForm System will be selected for this study based on previous performance. The Investigator and research staff will be familiar with the regulatory and good clinical practice requirements necessary to conduct a clinical study and agree to conduct the study in accordance with their institutional review board policies and procedures and conditions of approval imposed by the FDA and reviewing IRB. The facility in which the research will be conducted must have the available resources and physical space to conduct the study.

16 Investigator and Site Training

Investigator and study personnel training will be the conducted by the Sponsor or designee at the site initiation visit prior to the enrollment of any study subjects per established AirXpanders standard operating procedure. To ensure proper device usage, uniform data collection, and protocol compliance, the Sponsor or designee will present a formal training session to the Investigator and all study site personnel which will review the instructions for use of the device, the investigational plan, instructions on data collection, methods for soliciting data from alternative sources, completion of case report forms, schedules for follow-up, and regulatory requirements. Detailed feedback regarding completion of forms will be provided by the Sponsor or designee through the regular site monitoring.

17 Monitoring of Investigational Sites

A properly trained and qualified representative of the Sponsor or designee shall monitor the progress of this study to assure adequate protection of the rights and safety of the subjects and the quality and integrity of the resulting data. The monitoring shall be performed in accordance with the FDA Guideline for Monitoring of Clinical Investigations and established AirXpanders Standard Operating Procedures. Sites will be previously qualified, to assure that the investigator has the appropriate facilities and sufficient time and experience to conduct the investigation. Site initiation visits will be completed prior to subject enrollment to ensure that all study personnel are properly trained and understand their obligations to conduct the study in accordance with the investigational plan and all applicable regulations. Initial monitoring visits will be scheduled following the

first subject enrollment and periodic monitoring visits will be scheduled at all active investigational sites throughout the clinical study. Additional review will be performed on a site-by-site basis, as warranted by the findings of previous monitoring visits. The monitoring is designed to assure that the clinical investigation is being conducted according to the protocol requirements, all applicable state and federal regulations, conditions imposed by the FDA, IRB policies and procedures and GCP guidelines. These visits will assure that all enrolled subjects meet inclusion/exclusion criteria and that proper informed consent procedures are being followed. In addition, the monitor will ensure that CRFs are complete and accurate, regulatory records are maintained, all reports of device malfunction and/or device or procedure related adverse events are reported as required and device accountability and device inventory are controlled. The site shall provide working space and access to the subject's medical records to the monitor for source verification.

18 Protocol Compliance

The study investigators are responsible for performing the study in compliance with the protocol. Non-adherence to the protocol is to be classified as a protocol violation, protocol deviation, or protocol exemption, as defined below:

18.1 Protocol Violation

A protocol violation is any non-adherence to the protocol that may result in significant additional risk to the subject (e.g., enrollment of a subject who does not meet the study criteria) or non-adherence to Good Clinical Practices (GCP) that may impact patient safety (e.g., failure to obtain proper consent prior to performing study procedures). Violations should be reported to the study Sponsor and the IRB within 5 working days if they occur.

18.2 Protocol Deviation

Protocol deviations are non-adherence to study procedures which does not result in additional risk to the subject (e.g., subject missed visit). Protocol deviations must be reported to the sponsor on the deviation log by the study monitors and to be reported to the IRB per local policy.

18.3 Protocol Exemption

The Sponsor may decide to provide a protocol exemption in cases in which it is determined that the subject does not meet specific criteria for entering or continuing in the study as defined by the protocol; however, in the opinion of the Investigator and the Sponsor, the subject would possibly benefit from participation, and participation would not impact the safety of the subject, the ability to interpret the data, nor the rights and well-being of the subject. Exemptions should be reported promptly to the IRB given the severity and circumstances of the incident; per local IRB policy.

19 Data Collection

19.1 Electronic Case Report Forms (eCRFs)

All study-related data collection will be recorded on Sponsor provided source worksheets and entered into electronic Case Report Forms (eCRFs) by designated site personnel within 7 days of the subject visit. Data entered in the eCRFs must be supported by source documentation and will be reviewed by the monitors. Any discrepancies will be noted by the monitor and resolved by the delegated site personnel. The original source documents will be filed at the investigational sites.

19.2 Subject Satisfaction and Usability Data

Subjects will complete a satisfaction and usability questionnaire at the post-explant visit. Subject satisfaction data will be collected via a standard 7 point Likert Scale. Subjects will be asked to determine overall satisfaction with the treatment and study, and will be asked a series of questions aimed at identifying any user issues with the AeroForm device.

19.3 Physician Satisfaction and Usability Data

Physicians will complete a satisfaction and usability questionnaire at the post-explant visit. Physician satisfaction data will be collected via a standard 7 point Likert Scale. Physicians will be asked to determine overall satisfaction with the treatment and study, and will be asked a series of questions aimed at identifying any user identified issues with the AeroForm device.

19.4 Photographs

A series of baseline and follow-up photographs of the treatment area will be taken by qualified study personnel using the AirXpanders Photography Protocol. The subject's faces will not be photographed and no identifiable subject information will be recorded on the photographs. The photographs may be cropped or re-sized for comparison purposes but otherwise will not be re-touched or altered in any way. Image files will be stored electronically by AirXpanders and indexed by subject identifier. Copies of subject photographic data will be filed electronically at the clinical sites.

19.5 Device Data Logs

Dosage Controllers will be returned to AirXpanders at the time of explant and the device logs will be downloaded from the controllers by AirXpanders personnel for data analysis. Data from the logs includes dosing, volume, and the calculated CO_2 permeation rate. Interim data may be downloaded from the Dosage Controllers during the course of the study, as necessary to assess subject usage or troubleshoot any device issues.

20 Source Documentation

Source documentation includes subject medical records, results of laboratory or radiographic testing, operative reports, photographs, and any records pertinent to the care of the subjects while participating in the study. Regulations require that Investigators maintain information in the study patient's medical records which corroborate the data entered on the eCRFs. Source data and worksheets must be maintained and made available as required by monitors and/or regulatory inspectors for source verification. Examples of source documentation include:

1. Medical history/physical condition of the study subject before involvement in the study sufficient to verify protocol entry criteria.
2. Medical record documenting that informed consent was obtained for the subject's participation in the study.
3. Description of device implantation procedure (material used, drugs administered during the procedure, date, time, clinical findings, including

supporting data, if needed.

4. Dated and signed notes for each study patient visit including results of examinations.
5. Description of adverse events and follow-up of the adverse events (minimally event description, severity, onset date, duration, relation to study device, outcome and treatment for adverse event).
6. Notes regarding relevant concomitant medications taken during the study (including start and stop dates).
7. Study patient's condition upon completion of or withdrawal from the study.

21 Data Management

The original source data will be maintained at the study site. The source data will be entered into a designated study database and be monitored by in-house sponsor and/or contracted data management personnel. The eCRF entries for each subject will be compared against the original source documents. Data queries will be issued to the site for resolution, as necessary to clarify discrepancies in the data. Queries will be verified by monitors and data management. Final validation of the data will be complete and the database locked prior to analysis of the data in accordance with AirXpanders Standard Operating Procedures to ensure the quality and integrity of the data.

22 Study Closeout

Upon completion of the clinical study (when all patients enrolled have completed the follow-up visits, data has been monitored and queries have been completed), the Sponsor or designee will notify the site of closeout and a study closeout visit will be performed. Site close out will be done per established AirXpanders standard operating procedures. All unused study devices and any unused study materials will be collected and returned to the Sponsor. The Monitor will ensure that the Investigator's regulatory files are up to date and complete and that any outstanding issues from previous visits have been resolved. Other issues which will be reviewed at this visit include: discussion regarding retention of study files, possibility of site audits, publication policy, and notifying the IRB of study closure.

23 Record Retention

All study records and reports will remain on file at the investigational sites for a minimum of 2 years after completion of the study and/or marketing clearance of the device. The Investigator must contact AirXpanders before the destruction of any records and reports pertaining to the study to ensure they no longer need to be retained. In addition, the Site Monitor should be contacted if the Investigator plans to leave the investigational site.

24 Audits/Inspections

In the event that audits are initiated by the Sponsor (or its designee), FDA or other regulatory authorities, the Investigator shall allow access to the original medical records and study records, and provide all requested information. In the event of FDA audit, the site should notify the Sponsor promptly.

25 Ethical and Regulatory Considerations

This study shall be performed in accordance with all applicable federal, state and local laws and regulations, including without limitation 21 CFR Parts 11, 50, 54, 56, and 812, the requirements of the Food, Drug and Cosmetics Act (the "FDCA") and similar or successor legislation, any policies issued or conditions imposed by the U.S. Food and Drug Administration (the "FDA"), the ICH Guidelines for Good Clinical Practice (the "GCP Guidelines") and the Health Insurance Portability and Accountability Act of 1996 ("HIPAA") and any regulations and official guidance promulgated thereunder. Patient confidentiality will be maintained throughout the clinical study in a way that ensures the information can always be tracked back to the source data. For this purpose, a unique patient identification code (ID number and patient name code) will be used that allows identification of all data reported for each patient. Data relating to the study might be made available to third parties (for example in case of an audit performed by regulatory authorities) provided the data are treated confidentially and that the patient's privacy is guaranteed.

References:

Ascherman JA, et al. XPAND Patient-Activated Controlled Tissue Expander System for Breast Reconstruction: A Multi-Center Randomized Controlled Clinical Trial. *Plast Reconstr Surg*. 2014: Oct; 134 (4 Suppl 1):93-4.

Argenta, LC. Reconstruction of the breast by tissue expansion. *Clin Plast Surg*, 1984: Apr; 11(2); 257:264.

Bergé, SJ. Tissue expansion using osmotically active hydrogel systems for direct closure of the donor defect of the radial forearm flap. *Plast Reconstr Surg*, 2001: Jul; 108(1): 1-5.

Connell, A. Patient Activated Controlled Expansion for Breast Reconstruction with Controlled Carbon Dioxide Inflation: A Feasibility Study. *Plast Reconstr Surg*, 2011: Oct; 128(4):848-52.

Connell, A. Patient-Activated Controlled Expansion for Breast Reconstruction Using Controlled Carbon Dioxide Inflation: Confirmation of a Feasibility Study. *Plast Reconstr Surg*, 2014: Oct; 134(4):503e-11e.

Jacobs, D, et al. C02-Based Tissue Expansion: A Study of Initial Performance in Ovine Subjects. *Aesthet Surg J.* 2012: Jan; 32(1):103-9.

Kuo JV, Ramsinghani NS, Evans GRD, et al. In Vivo Dose Measurements in the Post-Mastectomy Irradiation of a Patient with a Gas-Based Tissue Expander. ASTRO 2013.

Moni, J, et al. Dosimetric Impact of the AeroForm Tissue Expander in Post-Mastectomy Radiation Therapy: An Ex-Vivo Analysis. *Pract Radiat Oncol*. 2015: Jan-Feb; 5(1):e1-8.

Neumann, CG. The expansion of an area of skin by progressive distention of a subcutaneous balloon. *Plast Recontr Surg*, 1957: Feb; 19(2): 124-30.

Radovan, C. Breast reconstruction after mastectomy uisng the temporary expander. *Plast Reconstr Surg*, 1982: Feb; 69(2): 195-206.

Rembert JL, et al. Radiation testing of the AeroForm co2-based breast tissue expander implant. *Radiation Oncology*, 2013: 8:235.

Tran T, Ding W, Subramanian B, Melven L, Chao M, Farrow H, Baker C. A dosimetric analysis of the aeroform TM tissue expander in radiation therapy. *Int J Cancer Ther Oncol,* 2014; 2(3): 020316.

Widgerow, AD. Patient-controlled expansion: Applying a new technique to breast reconstruction. *Aesth Plast Surg*, 2007: 31: 299-305.

Zeidler K., et al. Patient Activated Controlled Tissue Expander System for Breast Reconstruction: A Prospective, Multicenter, Randomized, Controlled, Open Label Clinical Study – Preliminary Results. *Annals of Plastic Surgery*, 2014: May; (72 Suppl 1): S 51-5.