Meso BioMatrix™ Acellular Peritoneum Matrix Breast Reconstruction Feasibility Trial Protocol

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MESO-001

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G120040

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NCT01823107

Sponsor
DSM Biomedical
Exton, PA USA

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Protocol Approval	
_____	_____
Forde Hansell, Sr. Manager of Clinical Research DSM Biomedical	Date

Protocol Acceptance	
_____	_____
Investigational Site Principal Investigator	Date

CONFIDENTIAL

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1. PROTOCOL SUMMARY

Title: Meso BioMatrix Breast Reconstruction Feasibility Trial

Investigational Device Description: The Meso BioMatrix™ Acellular Peritoneum Matrix ("Meso BioMatrix) is a bioresorbable porcine mesothelium-derived surgical mesh intended for reinforcement of soft tissues. The device is supplied sterile in double-layer packages. Meso BioMatrix is replaced by host tissue during the healing process.

Clinical Investigation Intended Use: The Meso BioMatrix implant is intended for implantation to reinforce soft tissues where weakness exists in subjects requiring soft tissue repair and/or reinforcement during breast reconstruction surgery.

Design: Prospective, multi-center, single-arm, feasibility phase trial.

Purpose: Demonstrate the feasibility and initial safety of the Meso BioMatrix for the reinforcement of weak soft tissue during two-stage, tissue expander-assisted breast reconstruction.

Primary Hypothesis: Meso BioMatrix can be safely used to provide reinforcement for the weak inferior mastectomy skin flaps during two-stage, tissue expander-assisted breast reconstruction.

Enrollment: A total of 25 subjects.

Clinical Sites: 10 clinical sites in the United States will participate.

Subject Population: Subjects undergoing two-stage, tissue expander-assisted breast reconstruction meeting eligibility criteria.

Follow-up Visits:
- Office visits at 1 week and 2 weeks after Meso BioMatrix implantation followed by every 1 – 4 weeks for tissue expansion.
- Office visits at 1 week, 1 month, 3 months, 6 months and 12 months after the tissue expander is exchanged for a permanent breast implant.

Primary Endpoint: Rate of breast related adverse events throughout the follow-up period.

Secondary Endpoints:
- Rate of all serious adverse events throughout the follow-up period.
- Presence of host tissue integration into the Meso BioMatrix mesh at the time of tissue expander / implant exchange.
- Breast-Q™ Satisfaction with Breast score at the last follow-up visit.

Principal Investigator:
To be determined

Sponsor:
DSM Biomedical
735 Pennsylvania Drive
Exton, PA 19341

2. TRIAL TITLE

Meso BioMatrix Breast Reconstruction Feasibility Trial

3. INVESTIGATIONAL DEVICE

3.1. Meso BioMatrix™ Implant

The device under investigation is the Meso BioMatrix™ Acellular Peritoneum Matrix ("Meso BioMatrix")

3.2. Regulatory History of Device

The United States Food & Drug Administration ("FDA") cleared Meso BioMatrix for marketing via the 510(k) clearance pathway in May 2010 (K094061).

3.3. 510(k) Cleared Indication

Meso BioMatrix™ is intended for implantation to reinforce soft tissues where weakness exists in subjects requiring soft tissue repair, reinforcement in plastic and reconstructive surgery, and in the urological, gynecological, and gastroenterological anatomy including but not limited to the following procedures: reinforcement of primary closure such as suture line reinforcement and muscle flap reinforcement; hernia repair (e.g., hiatal, femoral, paracolostomy, umbilical), urethral and vaginal prolapse repair, colon and rectal prolapse repair, reconstruction of the pelvic floor, bladder support, and sacrocolposuspension.

3.4. Clinical Investigation Intended Use

The Meso BioMatrix™ implant is intended for implantation to reinforce soft tissues where weakness exists in subjects requiring soft tissue repair and/or reinforcement during breast reconstruction surgery.

3.5. Description of Device

The Meso BioMatrix™ implant is a resorbable surgical mesh intended to reinforce soft tissue where weakness exists. The implant is derived from porcine peritoneum and is supplied sterile in double layer packages. The implant is packaged dry and prior to use is hydrated with saline or autologous body fluids such as blood, bone marrow aspirate, or blood concentrates such as platelet rich plasma. Meso BioMatrix provides structural and mechanical support to weak soft tissue during the healing process. Meso BioMatrix is fully replaced with native tissue between 6 and 12 months.

4. BACKGROUND INFORMATION

4.1. Two-stage, Tissue Expander Assisted Breast Reconstruction

Following mastectomy, women may elect to have breast reconstruction with autologous tissue or breast implants. Two-stage, tissue expander assisted breast reconstruction is one of the common surgical methods that could be selected to reconstruct the breast. This method either begins immediately after the general surgeon completes the mastectomy (immediate breast reconstruction) or at some time afterward (delayed breast reconstruction). During the first stage of the breast reconstruction procedure, the plastic surgeon releases the pectoralis muscle from the chest wall in order to create a pocket for the prosthesis. Then, a tissue expander is implanted beneath the pectoralis muscle and partially inflated. The tissue expander is gradually filled with saline over several weeks or months. Once the desired breast volume has been achieved, the second stage of the reconstruction takes place. In the second stage, the tissue expander is removed and replaced with a permanent saline or silicone gel breast implant. Historically, surgeons placed the tissue expander and breast implant either completely or partially under the pectoralis muscle. However, these methods of breast reconstruction have been associated with

less favorable aesthetic outcomes[1,2]. Therefore, in the early 2000s, surgeons started using AlloDerm® Regenerative Tissue Matrix (LifeCell Corporation, Branchburg, NJ), an acellular dermal matrix derived from human cadaveric tissue, to reinforce the inferior mastectomy skin flap and attempt to improve aesthetic outcomes[3]. Use of AlloDerm to reinforce the inferior mastectomy skin flap gives surgeons better control of the lower pole of the breast during reconstruction and has been associated with less pain, fewer tissue expansions and improved aesthetic outcomes[3-9]. However, AlloDerm adds significant cost to the procedure and some surgeons have seen an increased rate of post-operative complications such as infection, seroma, and hematoma when using AlloDerm[10-13], while others have seen no significant difference in the rate of complications with and without AlloDerm in tissue expander-assisted breast reconstruction[14,15]. It has been suggested that these increased risks may be related to the surgical technique learning curve[11], foreign body reaction or the fact that AlloDerm is considered aseptic but not sterile[13].

AlloDerm is regulated by the FDA according to the U.S. Code of Federal Regulations, Title 21, Part 1270 - Human Tissue Intended for Transplantation and Part 1271 - Human Cells, Tissues, and Cellular and Tissue-based Products. AlloDerm is indicated for repair or replacement of damaged or inadequate integumental tissue or for other homologous uses of human integument. Therefore, use of AlloDerm in breast reconstruction could be considered an off-label use. At present, there are no biologic surgical mesh devices approved or cleared by the FDA for use in breast reconstruction.

4.2. Relevant Systematic Literature Reviews

Three recent systematic literature review articles were published regarding the use of acellular dermal matrices ("ADM") during breast reconstruction. Jansen et al. tabulated adverse events from 14 relevant articles presenting outcomes after use of AlloDerm[16]. Newman et al. tabulated adverse events from 12 relevant articles reporting outcomes after use of AlloDerm. It should be noted that 3 of those 12 articles included 3 other biologic mesh devices along with AlloDerm[17]. Hoppe et al. tabulated adverse events from 7 relevant articles comparing outcomes with and without the use of AlloDerm during breast reconstruction[13]. The adverse events tabulated in their systematic reviews are compared in Table 1.

Table 1: Adverse Events Listed Systematic Review Articles for Breast Reconstruction

Adverse Event Term	**Jansen et al.*** (AlloDerm only)	**Newman et al.** (ADM)	**Hoppe et al.** (AlloDerm only)
Breast Reconstruction	# of Implants = 655	# of Implants = 789	# of Implants = 977
Infection	0 - 11%	5.2%	7.6%
Seroma	0 - 9%	6.0%	9.4%
Necrosis	0 - 25%	9.4%	Not reported
Hematoma	0 - 6.7%	Not reported	1.4%
Exposure w/ Prosthesis Loss	0 - 14%	Not reported	Not reported
Exposure w/ Prosthesis Salvage	0 - 4%	Not reported	Not reported
Capsular Contracture	0 - 8%	Not reported	Not reported

* Only probability ranges were presented due to limitations in underlying data

Jansen et al. and Hoppe et al. compared the rates of AlloDerm associated adverse events to adverse events in breast reconstruction without a biologic mesh. Jansen et al. found comparable rates of adverse events when a biologic mesh is used for breast surgery versus no biologic mesh use. However, Hoppe et al. found higher rates of adverse events when AlloDerm is used, but concluded that AlloDerm use may lead to greater patient satisfaction. It is important to note that the majority of articles in the above systematic review articles were retrospective, single-center

experiences. Such articles are prone to bias since adverse events are usually not uniformly defined and documented. Therefore, the true incidence of complications may have been underreported in the studies included in the above systematic reviews.

The potential benefits to AlloDerm assisted breast reconstruction cited in these systematic review articles are:

- Increased initial tissue expander fill volume[13]
- Reduced operative time[13]
- Reduced time to full expansion[13,16,17]
- Reduced time from tissue expander to breast implant exchange[16]
- Reduced post-operative and tissue expansion pain[13,16]
- Improved aesthetic outcome[16,17]
- Less capsular contracture[16]

The aforementioned authors all concluded that the potential benefits, when balanced with the potential complications, warrant additional study of the use of biologic surgical mesh for breast reconstruction.

4.3. Preclinical Testing

In-vitro bench tests and in-vivo animal studies have been performed to assess the safety and effectiveness of Meso BioMatrix for soft tissue repair and reinforcement. The pre-clinical testing demonstrated that the device is biocompatible and is replaced by native tissue during the healing process. A summary of the pre-clinical testing can be found in the Report of Prior Investigations in the Investigational Device Exemption ("IDE") application. The Report of Prior Investigations will be provided separately to the investigational sites along with the Investigational Plan.

4.4. Justification for the Trial

There exists a clinical need for a bioresorbable surgical mesh to support the lower pole of the breast during breast reconstruction. The ideal bioresorbable surgical mesh should be associated with a low rate of complications and a high rate of aesthetic success, while being cost effective to the subject and healthcare system. DSM Biomedical has developed a sterile bioresorbable surgical mesh with mechanical and handling properties similar to AlloDerm. This product may provide similar benefits as those associated with the use of AlloDerm during breast reconstruction and may reduce the risk of post-operative complications associated with AlloDerm. Therefore, a well-designed feasibility trial is warranted to evaluate the feasibility and initial safety of the use of Meso BioMatrix during breast reconstruction.

5. TRIAL INTRODUCTION

5.1. Trial Design

The trial is designed as a prospective, multi-center, single-arm, feasibility phase trial of subjects undergoing two-stage, tissue expander-assisted breast reconstruction.

5.2. Primary Trial Hypothesis

Meso BioMatrix can be safely used to provide reinforcement for the weak inferior mastectomy skin flaps during two-stage, tissue expander-assisted breast reconstruction.

5.3. Purpose

The purpose of the trial is to demonstrate the feasibility and initial safety of the Meso BioMatrix for the reinforcement of weak soft tissue during two-stage, tissue expander-assisted breast reconstruction.

5.4. Trial Objectives

The primary objective of this trial is to demonstrate the feasibility and initial safety of the Meso BioMatrix when use during breast reconstruction. If successful, the data collected in the feasibility phase trial may be used to support an IDE supplement for a pivotal phase trial.

5.5. Primary Endpoint

The primary endpoint of this feasibility phase trial is the rate of post-operative breast related adverse events through 12 months after the second stage of the breast reconstruction.

5.5.1. Primary Endpoint Justification

The primary endpoint of breast related adverse events provides an objective means to assess the initial safety of the Meso BioMatrix implant when used during breast reconstruction.

5.6. Secondary Endpoints

The secondary endpoints that will be evaluated in this trial are:

- Rate of all serious adverse events after Meso BioMatrix implantation through 12 months after the second stage of the reconstruction;
- Presence of host tissue integration into the Meso BioMatrix mesh at the time of second stage of the breast reconstruction;
- Breast-Q Satisfaction with Breast score at the final post-operative trial visit.

5.7. Follow-Up Duration

Subjects enrolled in this trial will have trial required follow-up visits through 12 months after the second stage of the breast reconstruction. It is estimated that the second stage of the reconstruction will occur between 3 to 6 months after the first stage. Therefore, each subject will be followed for approximately 15 to 18 months after Meso BioMatrix implantation, which is approximately two times the duration of Meso BioMatrix bioresorption. The follow-up visits are to occur according to the follow-up schedule described in Section 7.6 of this protocol.

5.8. Endpoint Evaluation Criteria

5.8.1. Primary Endpoint Evaluation

At each operative and post-operative visit, Investigators will document the presence or absence of breast related adverse events occurring since the prior visit. All breast related adverse events documented during trial-required visits will be recorded on the trial case report form. When one or more breast related adverse events are reported at one or more of the follow-up visits for an individual subject, the occurrence of the primary endpoint will be documented for that subject.

5.8.2. Secondary Endpoint Determination

The occurrence of each of the secondary endpoints will be determined as follows:

- At each visit, starting with the Meso BioMatrix implantation visit, Investigators will document the presence or absence of serious adverse events. All serious adverse events will be recorded on the trial case report form. When a serious adverse event is recorded at one or more follow-up visits for an individual subject, the occurrence of this secondary endpoint will be documented for the subject.
- During the second stage of the breast reconstruction, the tissue expander is surgically removed and replaced with a permanent breast implant. This second surgery provides the Investigator with an opportunity to visually inspect the condition Meso BioMatrix implant and take biopsies to assess the type and degree of host tissue integration within the implant. The biopsies taken during the second stage of the reconstruction will be preserved and sent to a central core laboratory for standardized analysis. If host tissue is found within an individual subject's biopsy specimen, than the occurrence of this secondary endpoint will be documented for the subject.

- At the 6 and 12-month visits after the second stage of the breast reconstruction, subjects will complete the Breast-Q Satisfaction with Breast survey. Each Breast-Q survey will be scored according to the author's instructions. Descriptive statistics will be presented for the Breast-Q Satisfaction with Breast scores at 6 and 12 month after the second stage of the reconstruction.

5.9. Number of Subjects to be Enrolled

A total of 25 subjects will be enrolled in this trial. The maximum allowable enrollment by a single clinical investigator is 15 subjects.

5.10. Participating Clinical Sites

5.10.1. Number of clinical sites

Ten (10) clinical sites will participate in the trial.

5.10.2. Investigator Names and Contact Information

The names, addresses and professional positions of each clinical site Principal Investigator as well as the name and address of each Institutional Review Board (IRB) Chairman for each site at which the investigation will be conducted is included in Section 8 of the Investigational Plan.

5.10.3. Investigator Training and Experience Requirements

All Investigators are board-certified plastic surgeons experienced in two-stage, tissue expander-assisted breast reconstruction surgery. All Investigators will receive "hands-on" training on the Meso BioMatrix implant prior to their first use.

5.11. Control Population

As this trial is designed to assess the feasibility as well as the initial safety of Meso BioMatrix during breast reconstruction, no control arm population is planned.

5.12. Minimization of Bias

As this is a single arm feasibility trial of a surgically implanted device, subject and surgeon investigator blinding is not possible. However, bias will be minimized by the following methods:

- A validated subjective patient reported outcome instrument is being used to assess aesthetic outcome.
- An independent core laboratory will conduct standardized evaluation of the biopsy specimens.
- Subjects will be screened and enrolled prospectively.
- Standardized definitions of all elements of the primary endpoint are provided to the investigators in section 8 of this protocol.

5.13. Duration of the Investigation

Due to the inclusion and exclusion criteria for this trial, subject enrollment is expected to be difficult. Therefore, recruitment of 25 subjects at 10 clinical sites is projected to last for approximately 24 months. Subjects will be followed for approximately 15 to 18 months after implantation with Meso BioMatrix. Therefore, the duration of time from the first subject's enrollment to the last subject's last scheduled follow-up is approximately 42 months.

6. SUBJECT POPULATION

6.1. Subject Selection-Criteria for Inclusion

Subjects that meet the following criteria of inclusion for this trial will be eligible to be recruited for this trial:

1. $\geq$ 21 years of age;
2. Female gender;
3. Subject is a non-smoker;

4. Subject is undergoing unilateral or bilateral, two-stage, tissue expander-assisted breast reconstruction;
5. Target breast(s) has well vascularized skin flaps;
6. Subject has a life expectancy greater than 18 months;
7. Subject agrees to return for the trial required follow-up visits; and
8. Subject provides written informed consent.

6.2. Subject Selection-Criteria for Exclusion

Candidates will be excluded from the trial if **any** of the following conditions apply:

1. Subject has a body mass index ≥ 35;
2. Subject had prior reconstructive breast surgery, breast augmentation, mastopexy or reduction mammoplasty on the target breast(s);
3. Subject has known or suspected infection at the surgical site;
4. Subject has a history of chronic corticosteroid use;
5. Subject has insulin dependent diabetes mellitus;
6. Subject has known or suspected disease or disorder putting the subject at a high risk for adverse events or procedural failure (e.g. HIV, collagen disease, connective tissue disorder, etc.);
7. Subject requires radical mastectomy;
8. Subject has a history of radiation therapy to the chest;
9. Subject's breast cancer is known to need post-operative treatment with adjuvant radiation therapy during the follow up period;
10. Subject treated with pre-operative induction chemotherapy for her breast cancer. Note,, treatment with neoadjuvant chemotherapy is acceptable if the intent is to decrease localized breast tumor burden prior to mastectomy;
11. Subject has known or suspected metastatic malignancy;
12. Subject is pregnant or desires to become pregnant within 18 months following breast reconstruction;
13. Subject has known or suspected allergy or intolerance to porcine tissue;
14. Subject has religious or cultural objection to products of porcine origin; or
15. Subject is concurrently participating in an investigational drug or device trial that has not completed the follow-up period.
16. Subject's anatomy is not amenable to two-stage, tissue expander-assisted, breast reconstruction with biologic surgical mesh reinforcement in the opinion of the Investigator.

7. TRIAL PROCEDURES, TESTS AND TREATMENTS

7.1. Informed Consent Requirements

The Investigator or a member of the research staff must obtain written informed consent from each prospective research subject. The template informed consent form for this trial was prepared in accordance with the U.S. Code of Federal Regulations, Title 21, Part 50.25: Elements of Informed Consent. The informed consent template is included in section 7 of the Investigational Plan. The informed consent form or a modification of it must have prior written approval from each clinical site's Institutional Review Board ("IRB"). All subjects must sign and date the most current IRB approved informed consent form prior to enrollment in the trial. Failure to provide informed consent renders a subject ineligible for the trial.

7.2. Subject Enrollment

Each subject providing informed consent that has passed all inclusion criteria and has no exclusion criteria present will be enrolled in the trial.

7.3. Surgical Procedure Descriptions

7.3.1. First Stage of the Breast Reconstruction

Surgeons will follow the Meso BioMatrix Instructions for Use included in Section 6 of the Investigational Plan. The surgical technique is summarized below:

- After mastectomy and confirmed hemostasis, the viability of the skin mastectomy skin flaps is assessed by visual inspection or imaging and addressed per standard of care.
- The inferior border of the pectoralis major muscle is elevated off the chest wall with blunt dissection and/or electrocautery in order to create a pocket for the tissue expander.
- Meso BioMatrix is hydrated with saline and, if necessary, tailored to the individual dimensions of the defect.
- Meso BioMatrix is oriented for implantation with the patterned, basal lamina side facing downward toward the tissue expander.
- Inferiorly, Meso BioMatrix is sutured to the chest wall in order to recreate the inframammary fold with 2-0 or 3-0 PDS™ II suture (Ethicon, Inc. Somerville, NJ). An interrupted suture pattern with approximately 2 cm between suture bites is recommended. The suture pattern will be recorded on the case report form.
- Superiorly, Meso BioMatrix is sutured to the lower pole of the released pectoralis major muscle with 2-0 or 3-0 PDS™ II suture. A continuous suture pattern is recommended. The suture pattern will be recorded on the case report form.
- A partially inflated, textured tissue expander is placed in the created subpectoral pocket.
- The tissue expander is filled until contact is achieved between the tissue expander and the Meso BioMatrix implant without subjecting the mastectomy skin flaps to undue tension. The volume will be adjusted if ischemia is noted in the skin flaps. The final initial fill volume will be recorded on the case report form.
- A closed suction drain is placed in the subcutaneous space between the skin and the Meso BioMatrix. The drain shall remain in place until output is less than 30cc in a 24-hour period. Placement of a second drain in the axilla or elsewhere in the breast is at the surgeon's discretion. The drain placement location(s) will be recorded on the case report form.
- Finally, the surgeon will close the surgical wounds according to his/her standard of care.
- Any adverse events or Meso BioMatrix malfunctions occurring during the procedure will be recorded on the case report form. A copy of the operative report will be collected from all first stage breast reconstruction procedures.

Note, if the subject is undergoing bilateral mastectomy and reconstruction, both breast reconstructions will be performed in the same fashion. Meso BioMatrix will be used for both breast reconstructions.

7.3.2. Tissue Expansion Phase

After the skin incision heals, expansion of the tissue expander begins. Patients will visit the Investigator approximately every 1 – 4 weeks for expansion until the desired expander fill volume is achieved.

7.3.3. Second Stage of the Breast Reconstruction

The second stage of the breast reconstruction is planned after the tissue expander(s) has reached the desired volume. The events that take place during the second stage of the breast reconstruction are summarized below:

- The surgeon will access and remove the tissue expander. The incision location will be recorded on the case report form.
- Biopsies of the Meso BioMatrix are taken from the pectoralis muscle interface, the center of the Meso BioMatrix, the inframammary fold interface and posterior to the expander. Biopsies will be placed in formalin, labeled and shipped to the Core Laboratory.
- A permanent saline or silicone implant will be placed within the pocket.

- If necessary, adjustments may be made according to the surgeon's standard of care in order to optimize the ultimate position of the breast implant and cosmetic result.
- The incisions will be closed according to the surgeon's standard of care.

Note, if the subject is undergoing bilateral reconstruction, the above events will also take place in the opposite breast. If the subject is having unilateral breast reconstruction, augmentation or mastopexy may occur in the opposite breast according to the surgeon's standard of care. If the subject elected to have nipple reconstruction during the second stage of the breast reconstruction, it will be done according to the surgeon's standard of care. A copy of the operative report will be collected for all second stage breast reconstruction procedures.

7.4. Trial Medication

Subjects in this trial will receive antibiotic prophylaxis consistent with the standard of care at each institution. The following antibiotic administration protocol is recommended for patients in this study:

- Within one hour prior to each surgery, subjects will receive 1 to 2 grams of Cefazolin (e.g. Ancef) intravenously[18].
- During the first and second stage surgeries, breasts will be irrigated with a triple antibiotic solution consisting of 1g of Cefazolin, 80mg of Gentamicin and 50,000 units of Bacitracin diluted in 1 liter of saline.
- After each surgery, subjects will take 1 – 2 grams daily of a first generation cephalosporin (e.g. cefadroxil, cephalexin) by mouth until the drains are removed, approximately 7 - 10 days.

In case of patient allergy to one or more of the antibiotics stated above or when surgery is performed in an institution with high rates of methicillin-resistant *Staphylococcus aureus* (MRSA), Investigators may substitute appropriate doses of appropriate alternative antibiotics (e.g. vancomycin pre-operatively[18]) for prophylaxis per his/her standard of care.

The type and frequency of antibiotics given to subjects will be collected on the case report form.

7.5. Required Tests and Evaluations

All subjects enrolled into this trial will undergo and have documented the below evaluations during designated visits. Table 2 displays the schedule for the study-required visits along with the required evaluations at each visit.

7.5.1. Medical History

A standard medical history will be documented in the subject's medical records before the breast reconstruction surgery to assess the subject for trial eligibility.

7.5.2. Biopsies

During the second stage of the breast reconstruction, four biopsy specimens will be obtained:

1. From the pectoralis muscle – Meso BioMatrix interface,
2. From the Meso BioMatrix centrally,
3. From the Inframammary fold – Meso BioMatrix interface, and
4. From the capsule posterior to the tissue expander as a control.

The size, location and method of biopsy collection, the method of specimen preservation and the method of specimen shipping will be provided separately by the core laboratory in the Core Laboratory Specimen Collection Manual.

7.5.3. Breast-Q™

The Breast-Q is a patient reported outcome instrument that has been validated for patients undergoing breast surgery[19,20]. The Post-operative Reconstruction Module of the Breast-Q will be used for this trial. Subjects will complete the Post-operative Reconstruction module of the

Breast-Q at 6 and 12 months after the second stage of the reconstruction. The Reconstruction module of the Breast-Q is copyright protected. It will be obtained and distributed to the clinical sites on a per patient and per use basis for use in the study.

7.5.4. Patient Diary

After the first stage of the breast reconstruction, Investigators or research coordinators will record the patient's post-operative level of pain, operative wound color, bruising, drain output, and pain medications taken on a daily basis until hospital discharge. After hospital discharge, patients will record their post-operative level of pain, operative wound appearance, bruising, drain output, pain medications taken and general comments (if any) on a daily basis in a patient diary until the 2-week post-operative visit. The patient diary will be collected by the Investigators or research coordinator at the 2-week post-operative visit.

7.5.5. Photographs

Photographs are required to be taken pre-operatively and at the last trial required follow-up visit (12 months after the second stage of the breast reconstruction). The pre-operative and last follow-up visit photographs provide visual documentation of the change in breast appearance during the trial. If the Investigator identifies a breast related adverse event during the follow-up period, photographs must be taken to document the type, location, and severity.

7.6. Schedule of Trial Required Visits and Visit Requirements

The required visits and the trial requirements at each visit are listed in Table 2 below.

Table 2: Schedule of Required Visits and Visit Requirements:

Required Visits	Visit Requirements
Pre-operative (Within 60 days pre-operative)	1. Medical History 2. Inclusion – Exclusion Criteria Screening 3. Photographs 4. Informed Consent
1st Stage of Reconstruction: Tissue Expander and Meso BioMatrix Implantation	1. Skin flap viability assessment 2. Adverse Event Assessment 3. Photographs, only if breast adverse event 4. Patient Diary given at discharge
1 Week Post 1st Stage Surgery (5 – 12 days)	1. Adverse Event Assessment 2. Photographs, only if breast adverse event
2 Weeks Post 1st Stage Surgery (12 – 21 days, not to be combined with 1st post-op visit)	1. Adverse Event Assessment 2. Photographs, only if breast adverse event 3. Collect patient diary
Tissue Expansion Visits (start after incision healing, then every 1 -4 weeks as tolerated until full expansion)	1. Tissue Expansion 2. Adverse Event Assessment 3. Photographs, only if breast adverse event
2nd Stage of Reconstruction: Tissue Expander – Implant Exchange (expected between 2 - 6 months after 1st stage)	1. Meso BioMatrix Biopsies 2. Adverse Event Assessment 3. Photographs, only if breast adverse event
1 Week Post 2nd Stage Surgery (5 – 14 days)	1. Adverse Event Assessment 2. Photographs, only if breast adverse event
1 Month Post 2nd Stage Surgery (23- 44 days)	1. Adverse Event Assessment 2. Photographs, only if breast adverse event
3 Months Post 2nd Stage Surgery (2 – 4 months)	1. Adverse Event Assessment 2. Photographs, only if breast adverse event
6 Months Post 2nd Stage Surgery (5 – 7 months)	1. Adverse Event Assessment 2. Photographs, only if breast adverse event 3. Breast-Q

Required Visits	Visit Requirements
12 Months Post 2nd Stage Surgery (11 – 13 months)	1. Adverse Event Assessment 2. Photographs 3. Breast-Q

Note, with the exception of obtaining biopsy specimens during the second stage of the reconstruction, all evaluations, procedures and follow-up visits for this trial are part of the standard of care for patients undergoing two-stage, tissue expander-assisted breast reconstruction.

7.7. Adjunctive Aesthetic Procedures

Two-stage breast reconstruction involves two separate surgical procedures. However, for some subjects, adjunctive procedures may be planned to optimize the aesthetic outcome following the second stage of the breast reconstruction. For example, in subjects whose mastectomy does not spare the nipple, a nipple reconstruction may occur during the second stage of the breast reconstruction or may be planned for a later surgical procedure. Additionally, some subjects may opt for adjustments to one or both breasts to optimize symmetry, fullness, etc. Therefore, one or more adjunctive aesthetic surgical procedures may be planned during the follow-up period in some subjects. Information about adjunctive aesthetic procedures to either breast will be recorded on the Adjunctive Aesthetic Procedure Form in the case report form. A copy of the operative report will be collected for all adjunctive aesthetic procedures involving the reconstructed breast(s). Adjunctive procedures for aesthetic issues will generally not meet the definition of a serious adverse event. See section 13.2 for the serious adverse event definition.

7.8. Unplanned Surgical Procedures

If any unplanned surgical procedures occur in the reconstructed breast(s) due to an adverse event or malfunction of the breast implant, tissue expander or Meso BioMatrix, the information from the unplanned procedures will be recorded on the Unplanned Surgical Procedure Form in the case report form. A copy of the operative report will be collected for all unplanned surgical procedures involving the reconstructed breast(s). Adverse events or device malfunctions requiring a surgical procedure will generally meet the definition of a serious adverse event. See section 13.2 for the serious adverse event definition and reporting requirements.

7.9. Reimbursement for Time and Travel

Subjects may receive up to $1000.00 as reimbursement for time, travel, and completion of study related documentation. The payment limits per visit are as follows:

Protocol Requirement	Payment
1 Week Post 1st Stage Surgery Visit	$100
2 Week Post 1st Stage Surgery Visit and return of the Patient Diary	$200
1 Week Post 2nd Stage Surgery Visit	$100
1 Month Post 2nd Stage Surgery Visit	$100
3 Month Post 2nd Stage Surgery Visit	$100
6 Month Post 2nd Stage Surgery Visit and completion of the outcome questionnaire	$200
12 Month Post 2nd Stage Surgery Visit and completion of the outcome questionnaire	$200

If a subject does not attend one of the above follow-up visits or does not complete the study documentation when required, then no payment will be made to the subject for that follow-up visit.

8. TRIAL DEFINITIONS

Asymmetry

An uneven appearance in terms of size, shape, or position between the two breasts.

Breast-related Adverse Events

Any untoward medical occurrence related to the reconstructed breast. Adverse events that meet this definition include but are not necessarily limited to:

- Infection
- Seroma
- Hematoma
- Tissue necrosis
- Dehiscence
- Red breast syndrome
- Allergic reaction
- Inflammatory response
- Meso BioMatrix failure
- Prosthesis extrusion
- Prosthesis (tissue expander or implant) failure
- Capsular contracture (grade 2-4)

Capsular Contracture

Defined as tightening of the tissue capsule around a breast implant. Capsular contracture is categorized according to the Baker capsular contracture grading system below:

- Grade I = Breast is normally soft and looks natural
- Grade II = Breast is a little firm but looks normal
- Grade III = Breast is firm and looks abnormal
- Grade IV = Breast is hard, painful, and looks abnormal

Device Failure

A device failure is a device malfunction that negatively impacts the treatment while used according to the labeling. For example, tearing of the Meso BioMatrix mesh resulting in an adverse event is a malfunction that negatively impacted the treatment.

Device Malfunction

The device does not meet its performance specifications or otherwise does not perform as intended.

Extrusion (implant or tissue expander)

Break down in the skin allowing the implant or tissue expander to appear through the skin.

Hematoma

Collection of blood beneath the skin.

Induction Chemotherapy

Initial treatment provided to patients who have an advanced stage of cancer usually treated with high doses of anticancer drugs (such as cisplatin or methotrexate). This can be for the purpose of attempting to cure the cancer entirely, or it might just be a preparation for other extensive surgery. Induction chemotherapy is given in cycles. Each cycle is followed by a rest period to help patients recover from the side effects of chemotherapy. This type of chemotherapy is mainly administered for six to twelve months until a patient achieves a stable state.

Malposition

Movement of the implant from the correct or intended position within the breast.

Mastectomy

Surgical removal of breast tissue. For this trial, the types of mastectomy will be categorized as follows:

- Nipple-sparing mastectomy: surgical removal of the breast tissues, but sparing the skin, nipple, and areola.
- Skin-sparing mastectomy: surgical removal of the breast tissues including the nipple and areola, but sparing most of the overlying skin.
- Total mastectomy: surgical removal of the breast including the nipple, areola, and most of the overlying skin.
- Modified radical mastectomy: surgical removal of the entire breast as well as the lymphatic tissue in the axilla.
- Radical mastectomy: surgical removal of the entire breast as well as the pectoral muscles, lymphatic bearing tissue in the axilla, and various other neighboring tissue.

Neoadjuvant Chemotherapy

Initial use of chemotherapy in patients with localized cancer in order to decrease the tumor burden prior to treatment by other modalities. A patient whose tumor can be removed by mastectomy, but first receives neoadjuvant chemotherapy to shrink the tumor enough to allow breast-conserving surgery, may therefore be eligible for this trial.

Non-smoker

A subject who either has:

- Never smoked.
- Smoked less than 100 cigarettes in his/her lifetime and had not smoked within 8 weeks prior to surgery.
- Smoked at least 100 cigarettes in his or her lifetime but who had quit smoking ≥ 8 weeks prior to surgery.

Red Breast Syndrome

Erythema in the reconstructed breast overlying the Meso BioMatrix that appears days to weeks after breast reconstruction without pain, elevated skin temperature, induration or elevated white blood cell count.

Severe Acute Inflammatory Response

An inflammatory response is protective response by the body to harmful stimuli. An acute inflammatory response is characterized by early onset of swelling, redness, heat and pain in the area of the harmful stimuli. Severe acute inflammatory response is characterized by substantial elevation of C-reactive protein and erythrocyte sedimentation rate, but white blood cell and neutrophil counts near or within normal limits. Inflammatory response versus infection is confirmed by negative microbiologic results from cultures obtained from the affected breast. A severe acute inflammatory response in this trial is an acute inflammatory response that requires removal of the investigational device.

Skin Necrosis
Dead skin or tissue.

Ptosis
Breast drooping or sagging. For this trial, the degree of ptosis will be classified according to the Regnault classification[21] as follows:
1. Mild ptosis: When the nipple areola complex is at the inframammary fold level.
2. Moderate ptosis: When the nipple areola complex is below the inframammary fold but over the lower edge of the breast.
3. Severe ptosis: When the nipple areola complex is below the inframammary fold and under the lower edge of the breast.
4. Pseudoptosis: When the nipple areola complex is above the inframammary fold but the whole breast tissue is located in the lower breast pole.

Serious Adverse Event
An adverse event that:
- is life threatening;
- results in permanent impairment of a body function;
- results in permanent damage to a body structure;
- necessitates medical or surgical intervention to preclude permanent impairment of a body function or permanent damage to a body structure; or
- results in hospitalization or prolongation of hospitalization.

Seroma
A fluid collection in a tissue location.

Surgical Site Infection
Erythema at the surgical incision in conjunction with a fever or an elevated white blood cell count.

9. RISK ANALYSIS

9.1. General Risks Associated with Surgery
The risks associated with surgery are described to subjects in the surgical consent form. Those potential complications are the following:
- Bleeding episodes during or after the procedure, in severe cases blood transfusion may be necessary;
- Swelling after the procedure;
- Pain after the procedure;
- Nerve damage causing numbness, tingling, pain and/or weakness in the affected area;
- Local or systemic allergic reactions to medications, surgical instruments, sutures and/or topical preparations used for the procedure;
- Venous or arterial thrombosis possibly leading to myocardial infarction, cerebrovascular accident or pulmonary embolism; and
- Complications from general anesthesia or surgery, which though very rare, could cause death.

9.2. Risks Associated with Tissue Expanders
The risks associated with tissue expanders during breast reconstruction are described to subjects in the surgical consent form provided separately by the surgeon. The risks associated with tissue expanders are[22-24]:
- Deflation;
- Tissue damage;
- Infection;

- Extrusion;
- Hematoma;
- Seroma;
- Capsular contracture;
- Premature explantation;
- Displacement;
- Compression on the bones of the chest wall;
- Pain;
- Dysesthesia (abnormal sensation);
- Distortion;
- Inadequate tissue flap; and
- Inflammatory reaction.

The occurrence of one or more of the above complications may require medical or surgical treatment, including additional surgery or tissue expander removal.

9.3. Risks Associated with Breast Implants

The risks associated with breast implants are described to subjects in the surgical consent form provided separately by the surgeon. Those complications that occur in ≥ 1% of patients receiving breast implants[25] are as follows:

- Asymmetry;
- Breast feeding difficulties;
- Breast pain;
- Ptosis;
- Calcification;
- Capsular contracture;
- Chest wall deformity;
- Deflation of the breast implant;
- Delayed wound healing;
- Extrusion;
- Hematoma;
- Iatrogenic injury or damage;
- Implant displacement or malposition;
- Implant palpability;
- Implant visibility;
- Implant wrinkling or rippling;
- Infection;
- Inflammation or irritation;
- Necrosis;
- Nipple or breast changes, including change in or loss of nipple sensation;
- Redness or bruising;
- Rupture of the breast implant;
- Scarring;
- Seroma;
- Skin rash;
- Lymphedema or lymphadenopathy;
- Breast tissue atrophy; and
- Unsatisfactory appearance due to implant style or size.

The occurrence of one or more of the above complications may require medical or surgical treatment, including additional surgery or implant removal.

9.4. Risks Associated with Biologic Surgical Mesh

The potential risks and benefits of participation in this trial are described in the subject informed consent form and are to be explained to the subject and/or their legal representative prior to participating in the trial.

The potential complications associated with the use of biologic surgical mesh during breast reconstruction are listed below. These complications are therefore also possible with the use of Meso BioMatrix during breast reconstruction. However, there may be unforeseen additional risks. The potential investigational device related complications are:

- Infection;
- Seroma;
- Hematoma;
- Tissue necrosis;
- Dehiscence;
- Erythema;
- Local or systemic allergic reaction to the Meso BioMatrix implant; and
- Defect Recurrence.

9.5. Risk Associated with Tissue Biopsy

During the second stage surgery, Investigators will obtain a total of four small biopsies: One at the Meso BioMatrix implant superior interface, one in the center of the Meso BioMatrix implant, one at the Meso BioMatrix implant inferior interface and one posterior to the expander. The risks associated with these tissue biopsies during the second stage surgery are:

- Infection at the biopsy location
- Bleeding at the biopsy location
- Weakening of the tissue surrounding the biopsy location

9.6. Risk Mitigation

In order to reduce the risk of potential adverse events to subjects recruited for this trial, subjects with higher surgical risk factors and known confounding risk factors have been excluded. In addition, subject subgroups that are known to have a reduced chance of a successful outcome (i.e. smokers, subjects undergoing peri-operative radiation therapy, obesity, etc.) due to confounding risk factors have been excluded from the trial.

Formal trial stopping rules have been defined in section 11.4.1 to assist with limiting exposure to the investigational device should known serious adverse events occur at a higher than expected rate or potentially unforeseen risks occur in study subjects.

It is expected that the investigational device implantation procedure will not add any significant additional operative time compared to the procedure as it is normally performed with AlloDerm or autologous tissue. In addition, the study required antibiotic regimens are consistent with the study investigators' standard of care.

Taking biopsies from the surgical mesh during the second stage surgery may increase certain risks. However, subjects will take prophylactic antibiotics to mitigate the risk of infection. Further, in the case of bleeding, surgeons can observe the biopsy sites during the second stage of the reconstruction and can address bleeding appropriately. Lastly, the biopsy specimens will be quite small relative to the surface area of the surgical mesh. Therefore, weakening of the mesh after biopsy is unlikely.

The Meso BioMatrix was designed and developed according to the Quality System Regulation. Device sterilization has been validated. Numerous in vivo animal studies have been conducted

with the Meso BioMatrix that demonstrated the biocompatibility, safety and effectiveness of the implant for soft tissue repair and reinforcement.

9.7. Anticipated Clinical Benefits

As described in the scientific literature, a majority of subjects who undergo tissue-expander assisted breast reconstruction with biologic surgical mesh experience improved aesthetic outcomes compared to tissue-expander assisted reconstruction without biologic surgical mesh or mastectomy alone. Therefore, it is expected that the majority of subjects in this trial will also experience satisfactory aesthetic outcomes. In addition, as reported in the AlloDerm literature, patients may experience less post-operative pain, reduced time to full expansion, reduced time between the first and second stage of the breast reconstruction and less capsular contracture as compared to two-stage, tissue-expander assisted reconstruction without a surgical mesh. The information gained from the conduct of this trial may be of benefit to other people with the same medical condition.

9.8. Alternative Treatments

Subjects do not have to participate in this trial to receive breast reconstruction surgery. There are alternative surgical methods available including direct to implant breast reconstruction, tissue expander-assisted implant reconstruction with an alternative biologic surgical mesh (albeit off-label), expander-assisted implant reconstruction without a biologic surgical mesh, and autologous flap reconstruction. These procedures each have different risk and benefit profiles. Subjects are informed about these alternative procedures in the informed consent form and are encouraged to discuss them with the Investigators.

10. TRIAL DATA COLLECTION, MONITORING AND QUALITY MANAGEMENT

10.1. Data Management

10.1.1. Clinical Trial Database

The clinical trial database will be compliant with Part 11 of Title 21 of the United States Code of Federal Regulations. Data type, range and logic verification edit checks will be programmed into the database.

10.1.2. Case Report Form

Clinical trial data were originally recorded on paper-based case report forms. Those case report forms were printed on 3-part NCR paper and provided in single patient binders. In the spring of 2014, the case report forms will become electronic for the remainder of the trial. The electronic case report form is eClinical OS™ (Merge Healthcare Incorporated located in Morrisville, NC).

10.1.3. Data Entry and Quality Control

Each field on the case report form will be entered into the clinical trial database. Each field will be subjected to data type verification and range checking, as appropriate. After a case report form page is entered into the database, a second staff member then compares the entered data to the case report form in order to identify discrepancies between the case report form and the clinical database. Any identified discrepancies are resolved within the database and the reason for data change is recorded in the data audit trail.

10.1.4. Data Cleaning and Editing

Periodic analysis of each data field across all entered subjects will be performed in order to identify omitted data, data discrepancies and outliers for possible data mistakes. Any discovered errors are then referred to the clinical site Research Coordinator or Investigator as a query on a data clarification form. The Research Coordinator or Investigator will review and respond to the query(s) on the data clarification form. Corrected data is entered in the clinical database and the reason for data change is recorded in the data audit trail.

10.1.5. Data Storage

The clinical trial database will reside on a secure server that will be backed up on a regular basis. Case report forms and data clarification forms will be stored in a secure storage room.

10.1.6. Trial Data Retention

Clinical trial data will be maintained by DSM Biomedical for no less than two years after the completion or termination of the trial or no less than two years after marketing application approval for the investigational device, whichever event occurs the latest. Clinical sites will be required to adhere to the same trial data retention period.

10.2. Clinical Site Initiation

When a site has fulfilled all relevant regulatory (i.e., FDA approval and IRB approval) and sponsor requirements (i.e., execution of a Clinical Research Trial Agreement, submission of required regulatory documents), a site initiation visit will be conducted. At the site initiation visit, the clinical site's Principal Investigator and Research Coordinator will receive training on the Investigational Plan and trial procedures.

10.3. Trial Data Monitoring

In order to assess the completeness and accuracy of the data provided by each site, the monitor will perform 100% source document verification of data in the case report form for each subject in the trial. The monitor will notify the Research Coordinator and/or Investigator of any data discrepancies between the source medical records and the case report form found during monitoring. When all fields on an individual case report form page have been verified, the monitor will initial and data the "Source Document Verification" box at the bottom of the page. The top two copies of each case report form page will be removed and submitted to data management.

10.4. Clinical Site Closeout

When all clinical data from each clinical site have been monitored and cleaned, a site closeout will be conducted. At the closeout, the monitor will verify that clinical data for all subjects are present and all required regulatory documents are present and up to date. Lastly, the monitor will ensure that the clinical site understands their trial data retention responsibilities.

11. STATISTICAL CONSIDERATIONS

11.1. Sample Size Justification

This is a feasibility trial with no formal statistical hypothesis. Therefore, the sample size of 25 subjects was empirically chosen.

11.2. Statistical Analysis

11.2.1. Data Presentation

All clinically relevant demographic, baseline, procedure and outcome variables will be summarized by scheduled visit using frequency tables and descriptive statistics as appropriate in accordanace with sections 8.2, 8.3, 8.4, 8.7 and 8.8 of the Guidance for Industry and FDA Staff – Saline, Silicone Gel and Alternative Breast Implants[26].

11.3. Interim Analysis Plans

There will be no interim analysis.

11.4. Criteria for Trial Termination

All serious adverse events and unanticipated adverse device effects reported during the trial will be evaluated to determine if the investigational device poses an unacceptable risk to subjects. If an unacceptable risk is determined in the judgment of the Investigators, the sponsor and/or the U.S. Food & Drug Administration, enrollment in the trial will be suspended while an

investigation into the cause of the unacceptable risk is undertaken. If the unacceptable risk cannot be mitigated by modifications to the investigational device or the investigational plan, the trial will be terminated.

11.4.1. Stopping Rules Related to the Investigational Device

DSM Biomedical will follow the below formal stopping rules in order to assure that enrollment will be suspended in a timely manner should potential serious safety issues arise unique to the investigational device:

- A serious immune reaction requiring surgical revision/removal of the investigational device occurs in 2 subjects.
- An investigational device malfunction requiring post-operative surgical revision/removal of the investigational device occurs in 3 subjects.
- A serious adverse event potentially related to the investigational device occurs in 5 subjects.
- A serious unanticipated adverse device effect is determined to have occurred.

Should one of the above stopping criteria occur, DSM Biomedical shall suspend enrollment as soon as possible, but not later than 5 working days after the determination that a stopping rule criterion has been met. The trial will remain suspended until the FDA and the each IRB have approved trial resumption.

11.4.2. Success Criteria

The purpose of this study is to demonstrate the safety and feasibility of the use of the Meso BioMatrix device when used for two-stage, tissue-expander assisted breast reconstruction. In order to warrant further study of the use of Meso BioMatrix device during breast reconstruction, the complications seen in this study should not be significantly greater than the complications seen in the AlloDerm literature. As described in the three recent systematic literature reviews cited in section 4.2 of this protocol, the rates of individual breast related adverse events associated with the use of AlloDerm are variable and, due to the retrospective nature of many of the articles in the AlloDerm literature, are likely underreported. Nonetheless, the AlloDerm literature provides a basis for assessing the initial safety of the Meso BioMatrix device. Based on the AlloDerm literature (reference section 4.2), the below rates of individual Meso BioMatrix related adverse events will be considered clinically acceptable for this pilot phase trial and may support progression to a pivotal phase trial:

- 0% rate of death,
- 0% rate of anaphylaxis,
- $\leq$ 8% rate of severe acute inflammatory response,
- $\leq$ 12% rate of infection,
- $\leq$ 20% rate of flap necrosis,
- $\leq$ 10% rate of Baker Grade 4 capsular contracture in breasts that do not receive post-operative radiation therapy.

12. TRIAL ADMINISTRATION

12.1. Trial Principal Investigator

To be determined

12.2. Sponsor

DSM Biomedical
735 Pennsylvania Drive
Exton, PA 19341 USA
Phone: 484-713-2100
Fax: 484-713-2900

12.3. Trial Monitor(s)

Forde Hansell
Sr. Manager, Clinical Research
DSM Biomedical
735 Pennsylvania Drive
Exton, PA 19341 (USA)
Phone: 484-713-2152
Fax: 484-713-2903

Novella Clinical
1700 Perimeter Drive
Morrisville, NC 27560 (USA)
Phone: 919-308-2168
Fax: 919-484-7727

12.4. Data Management

Novella Clinical
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Morrisville, NC 27560 (USA)
Phone: 919-308-2168
Fax: 919-484-7727

12.5. Core Laboratory

PPD Central Labs
2 Tesseneer Drive
Highland Heights
KY 41076- 9167 (USA)
Phone: 910-558-4807
Fax: 859-781-9310

13. ADVERSE EVENT REPORTING

13.1. Adverse Events

At each evaluation, the investigator will determine whether any adverse events (AEs) have occurred, whether expected or not. Adverse events occurring between required study visits will be recorded on the case report form of the next required visit. For the purpose of this protocol, an adverse event is any untoward medical occurrence in a subject. All AEs occurring during the trial period will be recorded in the case report form.

13.1.1. Adverse Event Severity

For the trial, the Investigators will categorize and report the severity of adverse events as follows:

- ***Mild*** = The AE is transient and easily tolerated by the subject.
- ***Moderate*** = The AE causes the subject discomfort and interrupts the subject's normal activities.
- ***Severe*** = The AE:
  - is life threatening;
  - results in permanent impairment of a body function or permanent damage to a body structure;
  - necessitates medical or surgical intervention to preclude permanent impairment of a body function or permanent damage to a body structure; or
  - results in hospitalization or prolongation of hospitalization.

13.1.2. Adverse Event Relatedness

The Investigators will also categorize and report the relatedness of the AEs as follows:

- ***Systemic*** = adverse events that are not related to the target breast (e.g. pulmonary embolus, allergic reactions to general anesthesia, illness, etc.)
- ***Related to Target Breast*** = adverse events that occur in or around the target breast that cannot be directly attributed to the implanted Meso BioMatrix (e.g. hematoma, pain, etc.).

- ***Related to Investigational Device*** = adverse events that may be directly linked to the implanted Meso BioMatrix.
- ***Related to Prosthesis*** = adverse events that may be directly linked to the tissue expander or breast implant.

13.1.3. Immediate Post-operative Symptoms as Adverse Events

Subjects in this trial will undergo two, possibly three, breast related surgeries. Pain, redness and swelling at the surgical site will occur in every subject following each surgery. Therefore, immediate post-operative symptoms and function restrictions will only be categorized as adverse events when a subject's complaint for any of these symptoms results in an unscheduled visit or when a subject presents with new or worsening symptoms as compared to the previous visit.

13.2. Serious Adverse Events

Serious adverse events ("SAEs") in this trial are adverse events that meet the definition of severe in section 13.1. All SAEs will be documented on the case report form. Investigators must also report SAEs to DSM Biomedical and the relevant Institutional Review Board within 48 hours of learning of the SAE. The Investigator shall make such notification to the sponsor on a Report of Serious Adverse Event in the case report form.

13.3. Unanticipated Adverse Device Effects

An unanticipated adverse device effect ("UADE") is defined as either:

- 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 problems associated with a device that relates to the rights, safety, or welfare of subjects.

Investigators must report UADEs to DSM Biomedical and the relevant Institutional Review Board within 48 hours of learning of the UADE. The Investigator shall make such notification on a Report of Serious Adverse Event form and document the UADE on the case report form. Following the report of the UADE, DSM will immediately conduct an investigation to determine the cause of the UADE and assess the level of risk to current and potential future research subjects. DSM will report the results of UADE evaluations, including any identified corrective actions, to FDA, all reviewing IRBs and all participating investigators within 10 working days after DSM first receives notice of the UADE. If DSM determines that the UADE presents an unreasonable risk to subjects based on a risk analysis, DSM shall terminate enrollment as soon as possible, but not later than 5 working days after this determination and not later than 15 working days after DSM first received notice of the UADE.

14. TRIAL RESPONSIBILITIES

14.1. General Responsibilities

14.1.1. Subject Confidentiality

Subject confidentiality is of utmost importance to all parties involved in this trial. DSM Biomedical, the Investigators, all assisting contract research organizations, monitors and the Core Lab will take appropriated steps to protect the identity of research subjects as stated in the HIPAA law.

14.1.2. Good Clinical Practice Guidelines

DSM Biomedical, the Investigators, all assisting contract research organizations, monitors and the Imaging Core Lab will follow Good Clinical Practice Guidelines (GCP) in the conduct of this trial.

14.2. Investigator Responsibilities

The investigator is responsible for ensuring the investigation is conducted according to all signed agreements and the Investigational Plan. This section further describes each Investigator's responsibilities.

14.2.1. Institutional Review Board (IRB) Approval

The investigator must submit the trial protocol to his/her IRB and obtain their written approval before being allowed to enroll subjects in the trial. The investigator is also responsible for fulfilling any conditions of approval imposed by the IRB, such as regular reporting, reporting of SAEs, etc.

14.2.2. Informed Consent Form

Part of the IRB approval must include approval of the Informed Consent Form specific to this trial. The investigator must administer the approved Informed Consent Form to each prospective trial subject, and obtain the subject's signature on the on the Informed Consent Form, prior to enrollment in the trial. The sample Informed Consent is included in section 7 of the Investigational Plan. The sample Informed Consent Form may be modified to suit the requirements of the individual site and IRB.

14.2.3. Protocol Compliance

Investigators must not deviate from the protocol. The only allowable exceptions are in cases of emergency to protect subject safety. All deviations from the protocol must be recorded in the case report form along with an explanation for the deviation. Continued deviations from the protocol may lead to termination of the investigator's participation in the trial.

14.2.4. Records

Each investigator must maintain current, precise and safeguarded records relating to the conduct of the investigation kept in a locked and restricted access area. These records include:

- correspondence with the IRB and the Sponsor,
- records of receipt, use and disposition of trial devices,
- records of each subject's trial participation.

Each investigator must retain the records of the investigation for at least 2 years after the completion of the trial or 2 years after the approval of a marketing application in the United States, whichever occurs last.

14.2.5. Reports

Investigators are responsible for reports of serious adverse events, unanticipated device effects, withdrawal of IRB approval, deviations from the investigational plan, use of the device without consent, progress reports and final reports. These reports must be submitted to the IRB and copies must be submitted to the Sponsor. Investigators must report serious adverse events and unanticipated adverse device effects to the sponsor with 48 hours of learning of the event.

14.3. Sponsor Responsibilities

DSM Biomedical is the sponsor of the trial. DSM Biomedical's responsibilities in the trial include:

14.3.1. Quality Assurance and Quality Control

Implement and maintain quality assurance and quality control to ensure the trial is conducted according to the Investigational Plan and applicable laws and regulations.

14.3.2. Investigational Plan Approval

Provide the Investigational Plan to the applicable regulatory authorities and to the Investigators. DSM Biomedical will ensure the Investigational Plan is approved by the applicable Institutional Review Board at each site prior to first subject enrollment.

14.3.3. Ensure Compliance with Investigational Plan and Regulations
DSM Biomedical will ensure the Investigators and all contracted parties comply with the Investigational Plan and all applicable regulations. If non-compliance is identified, DSM Biomedical shall take prompt and appropriate action to secure compliance or terminate the Investigator's or contracted party's participation in the trial.

14.3.4. Device Supply and Accountability
Provide properly labeled and packaged investigational devices to the participating trial sites in a quantity sufficient to support trial activities. DSM Biomedical will maintain a master record of all supplied, used, returned and destroyed investigational devices.

14.3.5. Device Training
Provide investigational device training to Investigators and trial site staff.

14.3.6. Investigator Selection
Select the Principal Investigator, all clinical investigators at the trial sites, and any consultants who participate in the trial. Eligible Investigators are those who are experienced in the treatment of the target population and who agree to allow direct access to trial records for the purpose of monitoring and auditing trial data.

14.3.7. Financial Support
Provide financial support at fair market value to the Investigators and/or personnel at the trial site in order to adequately conduct the trial.

14.3.8. Establish Regulatory Standards
Establish the regulatory standards to be followed for the clinical trial and other participants. All trial participants shall follow GCPs.

14.3.9. Monitoring Oversight
Assure site monitoring is performed in compliance with applicable regulations.

14.3.10. Safety Oversight
Monitor the safety of the use of the investigational device on an ongoing basis. If a significantly greater rate of SAEs or other adverse events are observed, it is the sponsor's responsibility to suspend enrollment in the trial to prevent subjects from being exposed to unnecessary risks while the root cause is being determined. DSM Biomedical shall promptly inform the Principal Investigator and the Site Principal Investigators about any UADEs occurring during the trial. Such notification shall be sent in writing.

14.3.11. Trial Reports
Provide annual progress reports and the final trial report to the Investigators and applicable regulatory authorities.

14.3.12. Trial Registration
Register the trial on the clinicaltrials.gov website if required in Title VIII of the Food and Drug Administration Amendments Act of 2007.

14.4. Monitor Responsibilities
The monitors are responsible for the following:

14.4.1. Ensuring Compliance with the Investigational Plan and Applicable Regulations
Ensure the rights, safety and welfare of trial subjects are being protected as required by the Investigational Plan and applicable regulations. Ensure the Investigators are complying with the procedures in the Investigational Plan. Ensure the Investigators are properly protecting and accounting for investigational devices. The monitor will also determine if the Investigator is maintaining the necessary regulatory documents.

14.4.2. Verifying Trial Data

Verify data on the case report form against the source documents for completeness and accuracy. Inform the Investigator and/or Research Coordinator of any discrepancies between the data on the case report form and the source documents and ensure appropriate corrections are made. Ensure all protocol deviations and adverse events are properly reported on the case report form.

15. PUBLICATION POLICY

DSM Biomedical retains ownership of all clinical data generated in this trial, and controls the use of the data for purposes of regulatory submissions. DSM Biomedical will exercise no veto over publication of trial results in the medical literature but must be provided with advance copies of manuscripts and abstracts to review for technical accuracy and confidential information. However, the Principal Investigator for the trial shall have first right of publication. No individual site experiences may be published prior to the principal trial manuscript without the expressed consent of the Principal Investigator and DSM Biomedical.

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