



Evidence-based Practice Center Systematic Review Protocol

Project Title: *Breast Reconstruction After Mastectomy*

I. Background and Objectives for the Systematic Review

Breast cancer is the most common new cancer diagnosis among women and the second most common cause of cancer death in the United States.¹ Approximately 268,600 new breast cancer diagnoses and 41,760 cancer-related deaths in the U.S. were estimated for 2019.² Surgery is a component of the standard treatment strategy for most patients with breast cancer. Surgical options include mastectomy (where the entire breast is removed) and lumpectomy or segmental mastectomy (where a portion of the breast is removed) followed by radiation. Mastectomy is chosen or recommended for approximately 50 percent of women in the U.S. with breast cancer.³

Breast reconstruction is commonly offered to women receiving mastectomy, and women are increasingly choosing to undergo breast reconstruction. As of 2016, more than 40 percent of women in the U.S. who underwent mastectomy had reconstruction.³ According to the American Society of Plastic Surgeons (ASPS)/Plastic Surgery Foundation, approximately 101,600 women in the U.S. underwent breast reconstruction in 2018.⁴ Federal regulations require that health insurance policies covering mastectomy also cover breast reconstruction.⁵

Two main considerations must be made once breast reconstruction surgery is chosen—**timing** and **type** of reconstruction. Breast reconstruction can be initiated either at the time of mastectomy (**immediate reconstruction**) or at a later date (**delayed reconstruction**). Immediate reconstruction is the most common practice in the U.S., selected for approximately 75 percent of patients.⁴ Immediate reconstruction is believed to be associated with better aesthetic results, lower overall costs, and better patient psychological well-being than delayed reconstruction.⁶ However, in the setting of postmastectomy radiation therapy, immediate reconstruction may be associated with more postoperative complications than delayed reconstruction.⁷

Based on the **type** of procedure or makeup of the newly reconstructed breast, reconstruction is categorized into **implant-based reconstruction (IBR)** and **autologous reconstruction (AR)**. Most reconstruction procedures in the U.S. (81%) are IBR, comprising **single-stage implant placements** and **two-stage implant placements**. In single-stage implant placement, also known as direct-to-implant placement, the implant placement is the only implantation procedure. In two-stage implant placement, a tissue expander is placed as a first procedure, followed by permanent implant exchange at a later date. Single-stage placements comprise 13 percent and two-stage procedures 68 percent of all reconstruction procedures; the remaining 19 percent of patients receive AR.⁴ **IBR** can be further divided based on the physical design of the implant (**silicone** vs. **saline**), the anatomic plane in which the device is placed (**total submuscular**, **partial submuscular**, and **prepectoral**), and whether an adjunctive **acellular dermal matrix (ADM)** is incorporated into the reconstruction.

Approximately 95 percent of implants for breast reconstruction used in the U.S. are silicone-filled because of the more natural feel and appearance and greater patient satisfaction than with saline implants.^{4, 8} While there are continued concerns and claims of potentially serious systemic problems related to silicone implants going back to the 1990s, based largely on case-control and animal studies,⁹⁻¹¹ a 2015 review by Balk et al. concluded that the evidence remained inconclusive about any association between silicone gel implants and long-term cancer or rheumatologic health outcomes.¹² However, breast implant-associated anaplastic large cell lymphoma (BIA-ALCL), an extremely rare type of non-Hodgkin's lymphoma, has been associated with silicone breast implants,¹³ leading to requests for recalls of specific silicone implant types.^{14,15}

The anatomic plane in which the implant is placed can have implications on complications, aesthetics, and cost. **Total submuscular placement** provides vascularized soft tissue coverage of the implant

without the need for adjuncts, such as ADM. But, total submuscular placement also has challenges, such as limits to the size of the breast reconstruction and incidence of “animation deformity”. Animation deformity, which refers to distortion of the reconstructed breast during contraction of the major pectoralis muscle, is experienced by as many as 80 percent of patients who receive total submuscular placement of the implant.^{16,17} To overcome these challenges, another option is that the implant can be **partial submuscular** placement with ADM, which has less risk of animation deformity, or **prepectoral** placement with ADM, which has no risk of animation deformity. Prepectoral placement also obviates the need for pectoralis muscle dissection and causes less pain.¹⁸ However, the prepectoral technique currently used is relatively novel, and evidence regarding comparative effectiveness, aesthetics, and harms of the various anatomic planes of implant placement is lacking.

ADMs, which can be derived from human (allografts), animal (xenografts), or synthetic sources, represent a heterogeneous group of biologic scaffolds that are used in reconstructive surgery. ADMs allow for repopulation, revascularization, and integration of the host’s cells into the implanted tissue.¹⁹ The use of ADMs may reduce the incidence of capsular contracture and may reduce the need for tissue expanders. The use of ADMs may also improve the aesthetic definition of the inframammary fold and medial border of the breast. However, ADMs might lead to more postoperative complications, such as infection and seroma.²⁰⁻²⁴ Regardless of the type of implant used, potential risks include infection, pain, capsular contracture, and implant rupture.¹⁴

With **AR**, breast reconstruction is done with the patient’s own tissue, thereby obviating the need for implants. In 2018, AR represented approximately 19 percent of breast reconstruction procedures performed in the U.S.⁴ AR is generally described by the anatomic region from where the tissue flap is sourced. These include deep inferior epigastric (DIEP; 52% of ARs), latissimus dorsi (LD; 22%), transverse rectus abdominis myocutaneous (TRAM; 21%), and others (5%).⁴ The source of the AR flap is limited by the patient’s body habitus, prior surgery, medical comorbidities, and preference. Different flaps vary in their type and frequency of complications. AR can have several advantages, including requiring only a single surgery (in contrast with the more common two-stage implant placement), reconstruction that is life-long (in contrast with the recommendation that implants be replaced every 10 years), and better long-term patient-centered outcomes, such as satisfaction, psychosocial wellbeing, and sexual wellbeing.²⁵ Compared with IBR, AR may be associated with higher patient satisfaction and fewer complications in patients undergoing postmastectomy radiation therapy.²⁶ But, AR requires a larger operation, leads to greater scarring, and may lead to long-term sequelae in the area of flap harvest and to more major complications, such as wound dehiscence and delayed healing.^{25,27}

Purpose of Review

This systematic review will assess the surgical breast reconstruction options for women who are undergoing (or have undergone) mastectomy for breast cancer. Specifically, the review will address the (comparative) benefits and harms of:

- IBR versus AR (Key Question [KQ] 1)
- Timing of IBR or AR in relation to chemotherapy and radiation therapy (KQ 2)
- Various options for IBR (KQs 3, 4, and 5)
- Various flap types for AR (KQ 6).

The intended audience for this systematic review includes guideline developers, plastic surgeons, breast surgical oncologists, medical oncologists, radiation oncologists, and other providers of care for women who have undergone (or are undergoing) mastectomy for breast cancer and are considering breast reconstruction. It is expected that the findings will inform clinical guidance for breast reconstruction after mastectomy.

II. Key Questions

- KQ 1: For adult women who are undergoing (or have undergone) mastectomy for breast cancer, what are the comparative benefits and harms of **implant-based (IBR) versus autologous (AR) breast reconstruction**?
- KQ 2: For adult women undergoing IBR or AR after mastectomy for breast cancer that requires either chemotherapy or radiation therapy, what is the **optimal time for IBR or AR with respect to**
- chemotherapy** or
 - radiation therapy**?
- KQ 3: For adult women undergoing IBR after mastectomy for breast cancer, what are the comparative benefits and harms of **different types of implants** (e.g., silicone, saline)?
- KQ 4: For adult women undergoing IBR after mastectomy for breast cancer, what are the comparative benefits and harms of **different anatomic planes of implant placement** (prepectoral, partial submuscular, and total submuscular)?
- KQ 5: For adult women undergoing IBR after mastectomy for breast cancer, what are the comparative benefits and harms of IBR **with versus without the use of a human acellular dermal matrix (ADM)** in the reconstruction procedure?
- KQ 6: For adult women undergoing AR after mastectomy for breast cancer, what are the comparative benefits and harms of **different flap types** for AR?

Contextual Questions:

Contextual Question 1:

What patient **preferences and values** inform decisionmaking about breast reconstruction after mastectomy for breast cancer? This includes the initial choice to undergo reconstruction, as well as the type and timing of surgery.

Contextual Question 2:

What **strategies or tools** (including shared decisionmaking) are available to help women make **informed choices** about breast reconstruction after mastectomy for breast cancer?

Study Eligibility Criteria

The specific eligibility criteria provided below have been refined based on discussions with a panel of Key Informants (KIs) and a Technical Expert Panel (TEP).

Key Question 1 (IBR Versus AR)

Population

- Adult (≥ 18 years old) women who are undergoing (or have undergone) mastectomy for any type of breast cancer (or carcinoma in situ) and have decided to undergo breast reconstruction
- Either therapeutic or prophylactic mastectomy
- Exclude: Studies where $\geq 10\%$ of women underwent breast reconstruction (combined across reasons):
 - for solely cosmetic purposes (i.e., augmentation)
 - for revision reconstruction (i.e., after a previous reconstruction for breast cancer)

Interventions

- IBR
 - Either single- or multi-stage
 - Any type of implant material, either smooth or textured, silicone or saline
 - Any anatomic plane of implant placement
 - With or without use of human ADM
 - With or without mastectomy and reconstruction of the contralateral breast (i.e., unilateral or bilateral)
 - With or without symmetry procedure (e.g., mastopexy) in the contralateral breast

Comparators

- AR using any flap (either free flap or pedicled), for example:
 - Deep inferior epigastric perforator (DIEP)
 - Latissimus dorsi (LD)
 - Transverse rectus abdominis myocutaneous (TRAM)
 - Superficial inferior epigastric artery perforator (SIEA)
 - Gluteal artery perforator (GAP)
 - Transverse musculocutaneous gracilis (TMG)
 - Transverse upper gracilis (TUG)
 - Profunda artery perforator (PAP)
- Combination of IBR and AR
- Exclude: Non-autologous flap transplants (i.e., cadaveric or xenotransplant)
- Exclude: Exclusive lipofilling/autologous fat reconstruction

Outcomes (* denotes important outcomes that will be used when developing Strength of Evidence tables)

- Quality of life*
- Physical well-being (e.g., pain, discomfort)*
- Psychosocial well-being (e.g., self-esteem, emotionality, normality)*
- Sexual well-being*
- Patient satisfaction with aesthetics (i.e., satisfaction with breast)*
- Patient satisfaction with outcome (e.g., satisfaction with care)*
- Planned staged surgeries for reconstruction
- Recurrence of breast cancer
- Harms

- Mortality*
- Unplanned repeat hospitalization*
- Duration of unplanned repeat hospitalization*
- Unplanned repeat surgeries – for revision of reconstruction (e.g., for asymmetry)*
- Unplanned repeat surgeries – for complications (e.g., for infection, bleeding)*
- Pain, including chronic pain*
- Analgesic (e.g., opioid) use*
- Necrosis, such as of the nipple or of the flap*
- Animation deformity*
- Complications that lead to delays in other cancer-related treatments (e.g., chemotherapy, radiation therapy)*
- Thromboembolic events*
- Infection
- Wound dehiscence
- Delayed healing
- Seroma
- Chronic conditions (e.g., rheumatologic diseases)
- Touch sensitivity
- Scarring

Potential Effect Modifiers:

- Age
- Stage of breast cancer
- First occurrence versus recurrent breast cancer
- Immediate versus delayed reconstruction
- Single-stage (direct to reconstruction) versus multi-stage (with tissue expander) reconstruction
- Unilateral versus bilateral reconstruction
- Radiation therapy versus no radiation therapy
- Chemotherapy versus no chemotherapy

Timing

- Any

Setting

- Any, including single- and multicenter

Design

- Randomized controlled trials (RCTs), $N \geq 10$ per group
- Nonrandomized comparative studies (NRCSs), $N \geq 30$ per group
- Case-control studies, $N \geq 100$ per group
- Single group studies, $N \geq 500$
- Studies may be prospective or retrospective
- Exclude: case reports and series of individually-reported case reports

Key Question 2 (Optimal Time For IBR or AR)

Population(s)

- Adult (≥ 18 years old) women who are undergoing IBR or AR after a mastectomy for breast cancer (or carcinoma in situ) that requires either chemotherapy or radiation therapy
- Either therapeutic or prophylactic mastectomy
- Exclude: Studies where $\geq 10\%$ of women underwent breast reconstruction (combined across reasons):
 - for solely cosmetic purposes (i.e., augmentation)
 - for solely prophylactic purposes (i.e., without diagnosed breast cancer)
 - for revision reconstruction (i.e., after a previous reconstruction for breast cancer)

Interventions

- a) IBR or AR before chemotherapy
- b) IBR or AR before radiation therapy
 - Either single- or multistage
 - With or without mastectomy and reconstruction of the contralateral breast (i.e., unilateral or bilateral)
 - With or without symmetry procedure (e.g., mastopexy) in the contralateral breast
 - With or without use of human ADM
 - For IBR – Any type of implant material, either smooth or textured
 - For IBR – Any anatomic plane of implant placement
 - For AR – Any flap type

Comparators

- a) IBR or AR after chemotherapy
- b) IBR or AR after radiation therapy

Outcomes (* denotes important outcomes that will be used when developing Strength of Evidence tables)

- Quality of life*
- Physical well-being (e.g., pain, discomfort)*
- Psychosocial well-being (e.g., self-esteem, emotionality, normality)*
- Sexual well-being*
- Patient satisfaction with aesthetics (i.e., satisfaction with breast)*
- Patient satisfaction with outcome (e.g., satisfaction with care)*
- Planned staged surgeries for reconstruction
- Recurrence of breast cancer*
- Harms
 - Mortality*
 - Unplanned repeat hospitalization*
 - Duration of unplanned repeat hospitalization*
 - Unplanned repeat surgeries – for revision of reconstruction (e.g., for asymmetry)*
 - Unplanned repeat surgeries – for complications (e.g., for infection, bleeding)*
 - Pain, including chronic pain*
 - Analgesic (e.g., opioid) use*
 - Necrosis, such as of the nipple or of the flap*
 - Animation deformity*
 - Complications that cause delays in other cancer-related treatments (e.g., chemotherapy, radiation therapy)*
 - Thromboembolic events*

- Infection
- Wound dehiscence
- Delayed healing
- Seroma*
- Chronic conditions (e.g., rheumatologic diseases)
- Touch sensitivity
- Scarring

Potential Effect Modifiers:

- Age
- Stage of breast cancer
- First occurrence versus recurrent breast cancer
- Type of chemotherapy (for KQ 2a) or radiation therapy (for KQ 2b)
- Immediate versus delayed reconstruction
- Single-stage (direct to reconstruction) versus multi-stage (with tissue expander) reconstruction
- Unilateral versus bilateral reconstruction

Timing

- Any

Setting

- Any, including single- and multicenter

Design

- RCTs, N \geq 10 per group
- NRCSs, N \geq 30 per group
- Case-control studies, N \geq 100 per group
- Single group studies, N \geq 500
- Studies may be prospective or retrospective
- Exclude: case reports and series of individually-reported case reports

Key Question 3 (Type of Implant Material)

Population(s)

- Adult (\geq 18 years old) women who are undergoing (or have undergone) mastectomy for any type of breast cancer (or carcinoma in situ) and have decided to undergo IBR
- Either therapeutic or prophylactic mastectomy
- Exclude: Studies where \geq 10% of women underwent breast reconstruction (combined across reasons):
 - for solely cosmetic purposes (i.e., augmentation)
 - for revision reconstruction (i.e., after a previous reconstruction for breast cancer)

Interventions

- IBR using one type of implant material
 - Saline
 - Silicone
 - Other materials

- Either smooth or textured
- Either single- or multistage
- Any anatomic plane of implant placement
- With or without use of human ADM
- With or without mastectomy and reconstruction of the contralateral breast (i.e., unilateral or bilateral)
- With or without symmetry procedure (e.g., mastopexy) in the contralateral breast

Comparators

- IBR using another type of implant material

Outcomes (* denotes important outcomes [i.e., unilateral or bilateral] that will be used when developing Strength of Evidence tables)

- Quality of life*
- Physical well-being (e.g., pain, discomfort)*
- Psychosocial well-being (e.g., self-esteem, emotionality, normality)*
- Sexual well-being*
- Patient satisfaction with aesthetics (i.e., satisfaction with breast)*
- Patient satisfaction with outcome (e.g., satisfaction with care)*
- Planned staged surgeries for reconstruction*
- Recurrence of breast cancer
- Harms
 - Mortality*
 - Unplanned repeat hospitalization*
 - Duration of unplanned repeat hospitalization*
 - Unplanned repeat surgeries – for revision of reconstruction (e.g., for asymmetry)*
 - Unplanned repeat surgeries – for complications (e.g., for infection, bleeding)*
 - Pain, including chronic pain*
 - Analgesic (e.g., opioid) use*
 - Necrosis, such as of the nipple*
 - Animation deformity*
 - Implant-related infections*
 - Implant rupture, including asymptomatic rupture*
 - Implant deflation*
 - Implant malposition*
 - Need for explant surgery*
 - Capsular contracture*
 - New neoplasms (e.g., BIA-ALCL)*
 - Complications that cause delays in other cancer-related treatments (e.g., chemotherapy, radiation therapy)*
 - Thromboembolic events*
 - Wound dehiscence
 - Delayed healing
 - Seroma
 - Chronic conditions (e.g., rheumatologic diseases)*
 - Touch sensitivity
 - Scarring
 - Red breast syndrome

Potential Effect Modifiers:

- Age
- Stage of breast cancer
- First occurrence versus recurrent breast cancer
- Immediate versus delayed reconstruction
- Single-stage (direct to reconstruction) versus multistage (with tissue expander) reconstruction
- Unilateral versus bilateral reconstruction
- Surface of implant (smooth versus textured)
- Shape of implant (round versus anatomic/teardrop)
- Size of implant (volume)

Timing

- Any

Setting

- Any, including single- and multicenter

Design

- RCTs, N \geq 10 per group
- NRCSSs, N \geq 30 per group
- Case-control studies, N \geq 100 per group
- Single group studies, N \geq 500
- Studies may be prospective or retrospective
- Exclude: case reports and series of individually-reported case reports

Key Question 4 (Anatomic Plane of Implant Placement)

Population(s)

- Adult (\geq 18 years old) women who are undergoing (or have undergone) mastectomy for any type of breast cancer (or carcinoma in situ) and have decided to undergo IBR
- Either therapeutic or prophylactic mastectomy
- Exclude: Studies where \geq 10% of women underwent breast reconstruction (combined across reasons):
 - for solely cosmetic purposes (i.e., augmentation)
 - for revision reconstruction (i.e., after a previous reconstruction for breast cancer)

Interventions

- IBR with implant placement in one anatomic plane
 - Prepectoral placement
 - Partial submuscular placement
 - Total submuscular placement
 - Either single- or multi-stage
 - Any type of implant material, either smooth or textured
 - With or without use of human ADM
 - With or without mastectomy and reconstruction of the contralateral breast (i.e., unilateral or bilateral)
 - With or without symmetry procedure (e.g., mastopexy) in the contralateral breast

Comparators

- IBR with implant placement in a different anatomic plane

Outcomes (* denotes important outcomes that will be used when developing Strength of Evidence tables)

- Quality of life*
- Physical well-being (e.g., pain, discomfort)*
- Psychosocial well-being (e.g., self-esteem, emotionality, normality)*
- Sexual well-being*
- Patient satisfaction with aesthetics (i.e., satisfaction with breast)*
- Patient satisfaction with outcome (e.g., satisfaction with care)*
- Planned staged surgeries for reconstruction*
- Recurrence of breast cancer
- Harms
 - Mortality*
 - Unplanned repeat hospitalization*
 - Duration of unplanned repeat hospitalization*
 - Unplanned repeat surgeries – for revision of reconstruction (e.g., for asymmetry)*
 - Unplanned repeat surgeries – for complications (e.g., for infection, bleeding)*
 - Pain, including chronic pain*
 - Analgesic (e.g., opioid) use*
 - Necrosis, such as of the nipple*
 - Animation deformity*
 - Implant-related infections*
 - Implant rupture, including asymptomatic rupture*
 - Implant deflation*
 - Implant malposition*
 - Need for explant surgery*
 - Capsular contracture*
 - New neoplasms (e.g., BIA-ALCL)*
 - Complications that cause delays in other cancer-related treatments (e.g., chemotherapy, radiation therapy)*
 - Thromboembolic events*
 - Infection*
 - Wound dehiscence
 - Delayed healing
 - Seroma
 - Chronic conditions (e.g., rheumatologic diseases)*
 - Touch sensitivity*
 - Scarring
 - Red breast syndrome

Potential Effect Modifiers:

- Age
- Stage of breast cancer
- First occurrence versus recurrent breast cancer
- Immediate versus delayed reconstruction
- Single-stage (direct to reconstruction) versus multistage (with tissue expander) reconstruction
- Unilateral versus bilateral reconstruction

- Surface of implant (smooth versus textured)
- Shape of implant (round versus anatomic/teardrop)
- Size of implant (volume)

Timing

- Any

Setting

- Any, including single- and multicenter

Design

- RCTs, N \geq 10 per group
- NRCSs, N \geq 30 per group
- Case-control studies, N \geq 100 per group
- Single group studies, N \geq 500
- Studies may be prospective or retrospective
- Exclude: case reports and series of individually-reported case reports

Key Question 5 (Use of Human ADM)

Population(s)

- Adult (\geq 18 years old) women who are undergoing (or have undergone mastectomy) for any type of breast cancer (or carcinoma in situ) and have decided to undergo IBR
- Either therapeutic or prophylactic mastectomy
- Exclude: Studies where \geq 10% of women underwent breast reconstruction (combined across reasons):
 - for solely cosmetic purposes (i.e., augmentation)
 - for revision reconstruction (i.e., after a previous reconstruction for breast cancer)

Interventions

- IBR with use of human ADM
 - Either single- or multistage
 - Any anatomic plane of implant placement
 - Any type of implant material, either smooth or textured
 - With or without mastectomy and reconstruction of the contralateral breast (i.e., unilateral or bilateral)
 - With or without symmetry procedure (e.g., mastopexy) in the contralateral breast

Comparators

- IBR without use of human or nonhuman ADM

Outcomes (* denotes important outcomes that will be used when developing Strength of Evidence tables)

- Quality of life*
- Physical well-being (e.g., pain, discomfort)*
- Psychosocial well-being (e.g., self-esteem, emotionality, normality)*
- Sexual well-being*
- Patient satisfaction with aesthetics (i.e., satisfaction with breast)*
- Patient satisfaction with outcome (e.g., satisfaction with care)*

- Planned staged surgeries for reconstruction*
- Recurrence of breast cancer
- Harms
 - Mortality*
 - Unplanned repeat hospitalization*
 - Duration of unplanned repeat hospitalization*
 - Unplanned repeat surgeries – for revision of reconstruction (e.g., for asymmetry)*
 - Unplanned repeat surgeries – for complications (e.g., for infection, bleeding)*
 - Pain, including chronic pain*
 - Analgesic (e.g., opioid) use*
 - Necrosis, such as of the nipple*
 - Animation deformity*
 - Implant-related infections*
 - Implant rupture, including asymptomatic rupture*
 - Implant deflation*
 - Implant malposition*
 - Need for explant surgery*
 - Capsular contracture*
 - New neoplasms (e.g., BIA-ALCL)*
 - Complications that cause delays in other cancer-related treatments (e.g., chemotherapy, radiation therapy)*
 - Thromboembolic events*
 - Infection*
 - Wound dehiscence*
 - Delayed healing*
 - Seroma*
 - Chronic conditions (e.g., rheumatologic diseases)
 - Touch sensitivity
 - Scarring
 - Red breast syndrome

Potential Effect Modifiers:

- Age
- Stage of breast cancer
- First occurrence versus recurrent breast cancer
- Immediate versus delayed reconstruction
- Single-stage (direct to reconstruction) versus multi-stage (with tissue expander) reconstruction
- Unilateral versus bilateral reconstruction
- Anatomic plane of implant placement (prepectoral versus partial submuscular versus total submuscular)
- Surface of implant (smooth versus textured)
- Shape of implant (round versus anatomic/teardrop)
- Size of implant (volume)
- Brand of human ADM (e.g., Alloderm[®], FlexHD[®], BellaDerm[®], AlloMax[®], Cortiva[®], DermACELL[®])

Timing

- Any

Setting

- Any, including single- and multicenter

Design

- RCTs, N \geq 10 per group
- NRCSs, N \geq 30 per group
- Case-control studies, N \geq 100 per group
- Single group studies, N \geq 500
- Studies may be prospective or retrospective
- Exclude: case reports and series of individually-reported case reports

Key Question 6 (Different Flap Types For AR)

Population(s)

- Adult (\geq 18 years old) women who are undergoing (or have undergone mastectomy) for any type of breast cancer (or carcinoma in situ) and have decided to undergo AR
- Either therapeutic or prophylactic mastectomy
- Exclude: Studies where \geq 10% of women underwent breast reconstruction (combined across reasons):
 - for solely cosmetic purposes (i.e., augmentation)
 - for revision reconstruction (i.e., after a previous reconstruction for breast cancer)

Interventions

- AR using one flap (either free flap or pedicled), for example:
 - Deep inferior epigastric perforator (DIEP)
 - Latissimus dorsi (LD)
 - Transverse rectus abdominis myocutaneous (TRAM)
 - Superficial inferior epigastric artery perforator (SIEA)
 - Gluteal artery perforator (GAP)
 - Transverse musculocutaneous gracilis (TMG)
 - Transverse upper gracilis (TUG)
 - Profunda artery perforator (PAP)
- With or without mastectomy and reconstruction of the contralateral breast (i.e., unilateral or bilateral)
- With or without symmetry procedure (e.g., mastopexy) in the contralateral breast
- Exclude: Non-autologous flap transplants (i.e., cadaveric or xenotransplant)
- Exclude: Exclusive lipofilling/autologous fat reconstruction

Comparators

- AR using a different flap (either free flap or pedicled)
- Combination of IBR and AR
- Exclude: Non-autologous flap transplants (i.e., cadaveric or xenotransplant)
- Exclude: Exclusive lipofilling/autologous fat reconstruction

Outcomes (* denotes important outcomes that will be used when developing Strength of Evidence tables)

- Quality of life*
- Physical well-being (e.g., pain, discomfort)*
- Psychosocial well-being (e.g., self-esteem, emotionality, normality)*

- Sexual well-being*
- Patient satisfaction with aesthetics (i.e., satisfaction with breast)*
- Patient satisfaction with outcome (e.g., satisfaction with care)*
- Planned staged surgeries for reconstruction*
- Duration of initial hospitalization*
- Recurrence of breast cancer
- Harms
 - Mortality*
 - Unplanned repeat hospitalization*
 - Duration of unplanned repeat hospitalization*
 - Unplanned repeat surgeries – for revision of reconstruction (e.g., for asymmetry)*
 - Unplanned repeat surgeries – for complications (e.g., for infection, bleeding)*
 - Pain, including chronic pain*
 - Analgesic (e.g., opioid) use*
 - Necrosis, such as of the nipple or of the flap*
 - Harms to area of flap harvest (e.g., hernia, bulge formation)*
 - Complications that lead to delays in other cancer-related treatments (e.g., chemotherapy, radiation therapy)*
 - Thromboembolic events*
 - Infection*
 - Wound dehiscence*
 - Delayed healing*
 - Seroma*
 - Touch sensitivity
 - Scarring

Potential Effect Modifiers:

- Age
- Stage of breast cancer
- First occurrence versus recurrent breast cancer
- Immediate versus delayed reconstruction
- Single-stage (direct to reconstruction) versus multi-stage (with tissue expander) reconstruction
- Unilateral versus bilateral reconstruction

Timing

- Any

Setting

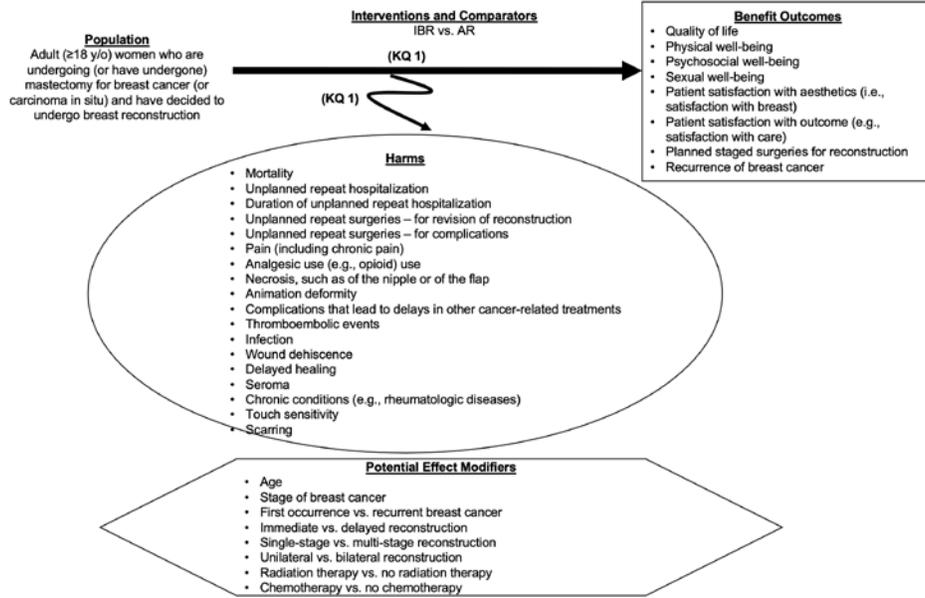
- Any, including single- and multicenter

Design

- RCTs, $N \geq 10$ per group
- NRCSs, $N \geq 30$ per group
- Case-control studies, $N \geq 100$ per group
- Single group studies, $N \geq 500$
- Studies may be prospective or retrospective
- Exclude: case reports and series of individually-reported case reports

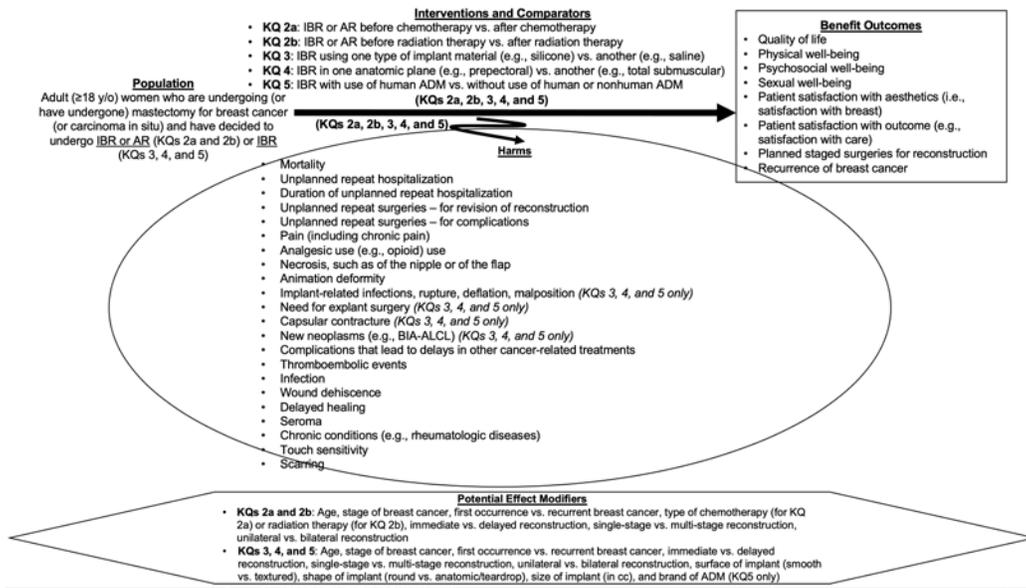
III. Analytic Frameworks

Figure 1. Analytic Framework for KQ 1: Implant-based versus autologous breast reconstruction



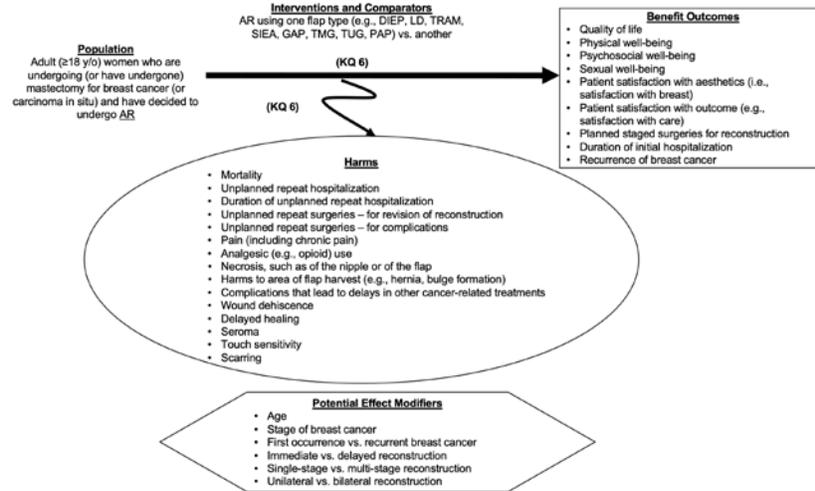
Abbreviations: AR = autologous reconstruction, IBR = implant-based reconstruction, KQ = Key Question

Figure 2. Analytic Framework for Key Questions focusing on timing of reconstruction (KQs 2a, 2b) and use of implants (KQs 3, 4, and 5)



Abbreviations: ADM = acellular dermal matrix, AR = autologous reconstruction, BIA-ALCL = breast implant-associated anaplastic large cell lymphoma, IBR = implant-based reconstruction, KQ = Key Question

Figure 3. Analytic Framework for KQ 6: Different flap types for autologous reconstruction



Abbreviations: AR = autologous reconstruction, DIEP = deep inferior epigastric perforator, GAP = gluteal artery perforator, KQ = Key Question, LD = latissimus dorsi, PAP = profunda artery perforator, SIEA = superficial inferior epigastric artery perforator, TMG = transverse musculocutaneous gracilis, TRAM = transverse rectus abdominis myocutaneous, TUG = transverse upper gracilis

IV. Methods

For all KQs, the systematic review will follow Evidence-based Practice Center (EPC) Program methodology, as laid out in its Methods Guide, particularly as it pertains to reviews of comparative effectiveness, diagnostic tests, and complex meta-analyses. As described below, the Contextual Questions will be addressed using a nonsystematic approach.

Conducting the Systematic Review (KQs 1-6)

Criteria for Inclusion/Exclusion of Studies in the Review: See Study Eligibility Criteria in Section II.

Literature Search Strategies to identify primary studies for all KQs: We will search for primary studies and systematic reviews in MEDLINE (via PubMed), Embase, The Cochrane Register of Clinical Trials, The Cochrane Database of Systematic Reviews, and CINAHL. Duplicate citations will be removed prior to screening. We will not employ any date or language restrictions to the search, but will include filters to remove nonhuman studies and articles that are not primary studies. We will include MeSH or Emtree terms, along with free-text words, related to breast, cancer, mastectomy, implants/implantation, and autologous reconstruction. The searches will be independently peer reviewed. Appendix A includes the search strategy for each database.

We will also run a search of the ClinicalTrials.gov registry for ongoing studies, unpublished study protocols, and unpublished study results. The reference lists of relevant existing systematic reviews will be screened for additional eligible studies. Additional articles suggested to us from any source, including peer and public review, will be screened applying identical eligibility criteria. Non-English language articles will be screened and data extracted either by readers of the relevant languages or after translation via Google Translate (<https://translate.google.com/>), if possible.

We will update the search upon submission of the draft report for public review.

Screening process: Citations from all searches will be deduplicated and then entered into Abstrackr software (<http://abstrackr.cebm.brown.edu/>) to enable title and abstract screening. The team will conduct two or more rounds of pilot screening. During each pilot round, we will all screen the same 100 abstracts and discuss conflicts, with the goal of training the team in the nuances of the eligibility criteria and refining them as needed. After the pilot rounds, we will screen all remaining abstracts in duplicate. The Abstrackr software has machine learning capabilities that predict the likelihood of relevance of each citation. Daily, the list of unscreened abstracts will be sorted so that the most potentially-relevant articles are presented first. This process will make screening more efficient and will enable us to capture the large majority of relevant articles relatively early in the abstract screening process.

Based on empirical research on Abstrackr (that is soon to be submitted for publication), when all remaining unscreened abstracts have a prediction value <0.40 (on a scale of 0 to 1), we will consider switching to single screening of remaining abstracts. The empirical research suggests that at this threshold, all remaining abstracts will be rejected. Typically, this threshold is reached when more than half the abstracts have been screened. We will consider stopping screening if there are no eligible citations identified in a consecutive sample of 370 consecutive citations (this sample size chosen because the upper 97.5% confidence interval bound for a proportion of $0/370$ is less than 1%).

Potentially relevant citations will be retrieved in full text. These articles will be rescreened in duplicate.

Data Extraction and Data Management: Data from eligible studies will be extracted into the Systematic Review Data Repository-Plus (SRDR-Plus) software (<https://srdplus.ahrq.gov>). Each article will be extracted by one researcher, and entered data will be confirmed by a second, independent researcher. Individual studies with multiple publications will be extracted as a single study (with a single entry in SRDR-Plus). Each study will be entered into SRDR-Plus separately, even if two or more studies are reported within a single publication.

For each study, we will extract publication identifying data, study design features, population characteristics, intervention and comparator names and descriptions, relevant outcomes and their definitions, and funding source. We will extract, as available, data on the effect modifiers that are relevant to the KQ(s) being addressed by each study.

Assessment of Methodological Risk of Bias of Individual Studies: We will evaluate each study for risk of bias and methodological quality.

Because we anticipate including a variety of study designs, we will incorporate items from three different existing commonly-used tools and will tailor the set of items for each study design. The three tools will include the Cochrane Risk of Bias Tool,²⁸ the Risk of Bias in Nonrandomized Studies (ROBINS-I) Tool,²⁹ and the National Heart, Lung, and Blood Institute (NHLBI) Quality Assessment Tool.³⁰

For RCTs, we will use all the items from the Cochrane Risk of Bias Tool,²⁸ focusing on issues related to randomization and allocation concealment methodology; blinding of patients, study personnel/care providers, objective outcome assessors, and subjective outcome assessors; incomplete outcome data; selective outcome reporting; and other issues that could be related to bias. We will also use items from the NHLBI Tool focusing on the adequacy of descriptions of study eligibility criteria, interventions, and outcomes.³⁰

For NRCSSs, we will use the specific sections of the ROBINS-I Tool²⁹ that pertain to confounding and selection bias. ROBINS-I requires the identification of specific confounders of interest for the systematic review. For the purpose of assessing for the presence of potential confounding in studies, we will consider as age, body mass index (BMI), and stage of breast cancer as potential confounders for all KQs. In

addition, we will consider history of abdominal surgeries as a potential confounder for KQ 6. Because NRCSs, like RCTs, can be impacted by the lack of blinding and by participant loss to followup, we will also use the items from the Cochrane Risk of Bias Tool²⁸ that focus on issues related to blinding of patients, study personnel/care providers, objective outcome assessors, and subjective outcome assessors; incomplete outcome data; selective outcome reporting; and other issues that could be related to bias. We will also use items from the NHLBI Tool that pertain to the adequacy of descriptions of study eligibility criteria, interventions, and outcomes.³⁰

For single-group studies, we will use the items from the Cochrane Risk of Bias Tool²⁸ that pertain to issues of participant loss to followup, specifically, incomplete outcome data, selective outcome reporting, and other issues that could be related bias. We will also use items from the NHLBI Tool focusing on the adequacy of descriptions of study eligibility criteria, interventions, and outcomes.³⁰

Data Synthesis: We will summarize the evidence both qualitatively and, when feasible, quantitatively. Each study included in the systematic review will be described in summary and evidence tables presenting study design features, study participant characteristics, descriptions of interventions, outcome results, and risk of bias/methodological quality. Summary tables will briefly describe the studies and their findings.

For all KQs, we will compare interventions with their comparators for their effects, primarily with odds ratios (ORs) for dichotomous outcomes (e.g., recurrence of breast cancer), net mean differences (NMDs) (between-intervention comparison of within-intervention changes) for continuous outcomes with both pre- and postintervention data (e.g., pain or quality of life scales), and differences (between interventions) in continuous outcome data postintervention (e.g., patient satisfaction with aesthetics). Where there are sufficient studies reporting sufficiently similar results, we plan to conduct pairwise meta-analyses. If data allow, we also plan to conduct network meta-analyses comparing the different interventions with each other and with placebo (or no intervention). Depending on the evidence base, we may conduct separate analyses by each effect modifier. We expect to summarize harms data semiquantitatively (i.e., without meta-analysis).

For all KQs, we expect to qualitatively describe reporting of differences in effects and harms by different subgroups, or predictors. We do not expect to be able to conduct statistical analyses on these evaluations. We expect to primarily rely on reported within-study differences in effects (or harms). However, we will look for opportunities to qualitatively or quantitatively compare results across studies.

Grading the Strength of Evidence (SoE) for Major Outcomes and Comparisons: We will evaluate the SoE addressing each major comparison or evaluation for each KQ. We expect that these will include the following comparisons for women undergoing reconstruction after mastectomy for breast cancer:

- Relative clinical effects of IBR versus AR
- Harms of IBR and AR
- Relative clinical effects of IBR or IR before versus after chemotherapy
- Harms of IBR or IR before and after chemotherapy
- Relative clinical effects of IBR or IR before versus after radiation therapy
- Harms of IBR or IR before and after radiation therapy
- Relative clinical effects of silicone versus saline implants for IBR
- Harms of silicone and saline implants for IBR
- Relative clinical effects of prepectoral, partial submuscular, and total submuscular placement of implants during IBR
- Harms of prepectoral, partial submuscular, and total submuscular placement of implants during IBR
- Relative clinical effects of use versus nonuse of human ADMs during IBR

- Harms of use and nonuse of human ADMs during IBR
- Relative clinical effects of various flap types for AR
- Harms of various flap types for AR

We will grade the strength of the body of evidence as per the Agency for Healthcare Research and Quality (AHRQ) Methods Guide on assessing SoE.^{31,32} We will assess SoE for each of the important clinical outcome categories. We determined the relative importance of the outcomes with input from the TEP. For now, these categories include recurrence of breast cancer, quality of life, physical well-being, psychosocial well-being, sexual well-being, patient satisfaction with aesthetics, and the harm-related outcomes of mortality, repeat hospitalization, unplanned repeat surgeries, pain, and necrosis, including nipple necrosis. For KQ 3 (types of implant for IBR) we will also include in the SoE tables the harm-related outcome of implant-related infections. For KQ 6 (flap types for AR) we will also include in the SoE tables harms to area of flap harvest. These outcomes that we are currently considering as important are consistent with the outcomes in a “core outcome set” that was published in 2015 for research on breast reconstructive surgery.^{33,34} Core outcome sets are agreed minimum sets of outcomes that should be reported in research in a given topic area.³⁵

For each SoE assessment, we will consider the number of studies, their study designs, the study limitations (i.e., risk of bias and overall methodological quality), the directness of the evidence to the KQs, the consistency of study results, the precision of any estimates of effect, the likelihood of reporting bias, other limitations, and the overall findings across studies. Based on these assessments, we will assign a SoE rating as being either high, moderate, low, or insufficient evidence to estimate an effect.

Outcomes with highly imprecise estimates, highly inconsistent findings across studies, or with data from only one study will be deemed to have insufficient evidence to allow for a conclusion (with the exception that a particularly large and generalizable single study could provide at least low SoE). This approach is consistent with the concept that for imprecise evidence “any estimate of effect is very uncertain,” the definition of Very Low quality evidence per GRADE.³⁶

We will summarize the data sources, basic study characteristics, and each SoE dimensional rating in a “Summary of Evidence Reviewed” table. This table will detail our reasoning for arriving at the overall SoE rating.

Assessing Applicability: For each KQ (or specific subquestion), we will assess the applicability of the included studies primarily based on the studies’ eligibility criteria and their included participants, specifically related to such factors as age, type of breast cancer, and first occurrence versus recurrent breast cancer. These will be qualitatively compared with typical distributions of these factors among patients undergoing breast reconstruction in the U.S.

Addressing the Contextual Questions

Based on data and input garnered during our systematic review of the KQs, we will answer the contextual question in a narrative format. We will not systematically extract or review eligible studies, create summary tables, or assess the strength of evidence for the Contextual Questions.

V. References

1. U.S. Department of Health and Human Services, Centers for Disease Control and Prevention and National Cancer Institute. U.S. Cancer Statistics Working Group. U.S. Cancer Statistics Data Visualizations Tool, based on November 2018 submission data (1999-2016). 2019.
2. American Cancer Society. Breast Cancer Facts & Figures 2019-2020. . 2019. <https://www.cancer.org/content/dam/cancer-org/research/cancer-facts-and-statistics/breast-cancer-facts-and-figures/breast-cancer-facts-and-figures-2019-2020.pdf>. Accessed on December 28, 2019.
3. Jonczyk MM, Jean J, Graham R, et al. Surgical trends in breast cancer: a rise in novel operative treatment options over a 12 year analysis. *Breast Cancer Res Treat.* 2019 Jan;173(2):267-74. doi: 10.1007/s10549-018-5018-1. PMID: 30361873.
4. American Society of Plastic Surgeons. 2018 Plastic Surgery Statistics Report. 2018. <https://www.plasticsurgery.org/documents/News/Statistics/2018/plastic-surgery-statistics-full-report-2018.pdf>. Accessed on December 28, 2019.
5. Employee Benefits Security Administration. Your Rights After a Mastectomy.; 2018. <https://www.dol.gov/sites/default/files/ebsa/about-ebsa/our-activities/resource-center/publications/your-rights-after-a-mastectomy.pdf>. Accessed on December 28, 2019
6. Al-Ghazal SK, Sully L, Fallowfield L, et al. The psychological impact of immediate rather than delayed breast reconstruction. *Eur J Surg Oncol.* 2000 Feb;26(1):17-9. doi: 10.1053/ejso.1999.0733. PMID: 10718173.
7. Wilkins EG, Hamill JB, Kim HM, et al. Complications in Postmastectomy Breast Reconstruction: One-year Outcomes of the Mastectomy Reconstruction Outcomes Consortium (MROC) Study. *Ann Surg.* 2018 Jan;267(1):164-70. doi: 10.1097/sla.0000000000002033. PMID: 27906762.
8. McCarthy CM, Klassen AF, Cano SJ, et al. Patient satisfaction with postmastectomy breast reconstruction: a comparison of saline and silicone implants. *Cancer.* 2010 Dec 15;116(24):5584-91. doi: 10.1002/cncr.25552. PMID: 21136577.
9. Greenland S, Finkle WD. A case-control study of prosthetic implants and selected chronic diseases in Medicare claims data. *Ann Epidemiol.* 1998 Jul;8(5):319-26. doi: 10.1016/s1047-2797(97)00212-3. PMID: 9669614.
10. Lewy RI. Laboratory findings reveal potential harm of breast implants. *Tex Med.* 1993 Dec;89(12):7. PMID: 8178307.
11. Schaefer CJ, Lawrence WD, Wooley PH. Influence of long term silicone implantation on type II collagen induced arthritis in mice. *Ann Rheum Dis.* 1999 Aug;58(8):503-9. doi: 10.1136/ard.58.8.503. PMID: 10419870.
12. Balk EM, Earley A, Avendano EA, et al. Long-Term Health Outcomes in Women With Silicone Gel Breast Implants: A Systematic Review. *Ann Intern Med.* 2016 Feb 2;164(3):164-75. doi: 10.7326/m15-1169. PMID: 26550776.
13. Rupani A, Frame JD, Kamel D. Lymphomas Associated with Breast Implants: A Review of the Literature. *Aesthet Surg J.* 2015 Jul;35(5):533-44. doi: 10.1093/asj/sjv016. PMID: 26116741.
14. U.S. Food and Drug Administration Center for Devices and Radiological Health. FDA Update on the Safety of Silicone Gel-Filled Breast Implants. 2011. <https://www.fda.gov/media/80685/download>. Accessed on April 9, 2020.
15. U.S. Food and Drug Administration. The FDA Requests Allergan Voluntarily Recall Natrelle BIOCELL Textured Breast Implants and Tissue Expanders from the Market to Protect Patients: FDA Safety Communication.; 2019. <https://www.fda.gov/medical-devices/safety-communications/fda-requests-allergan-voluntarily-recall-natrelle-biocell-textured-breast-implants-and-tissue>. Accessed on April 9, 2020.
16. Becker H, Fregosi N. The Impact of Animation Deformity on Quality of Life in Post-Mastectomy Reconstruction Patients. *Aesthet Surg J.* 2017 May 1;37(5):531-6. doi: 10.1093/asj/sjw264. PMID: 28158447.

17. Hanna KR, DeGeorge BR, Jr., Mericli AF, et al. Comparison study of two types of expander-based breast reconstruction: acellular dermal matrix-assisted versus total submuscular placement. *Ann Plast Surg.* 2013 Jan;70(1):10-5. doi: 10.1097/SAP.0b013e31822f6765. PMID: 21862915.
18. Walia GS, Aston J, Bello R, et al. Prepectoral Versus Subpectoral Tissue Expander Placement: A Clinical and Quality of Life Outcomes Study. *Plast Reconstr Surg Glob Open.* 2018 Apr;6(4):e1731. doi: 10.1097/gox.0000000000001731. PMID: 29876176.
19. Wainwright DJ. Use of an acellular allograft dermal matrix (AlloDerm) in the management of full-thickness burns. *Burns.* 1995 Jun;21(4):243-8. doi: 10.1016/0305-4179(95)93866-i. PMID: 7662122.
20. Dikmans RE, Negenborn VL, Bouman MB, et al. Two-stage implant-based breast reconstruction compared with immediate one-stage implant-based breast reconstruction augmented with an acellular dermal matrix: an open-label, phase 4, multicentre, randomised, controlled trial. *Lancet Oncol.* 2017 Feb;18(2):251-8. doi: 10.1016/s1470-2045(16)30668-4. PMID: 28012977.
21. Negenborn VL, Young-Afat DA, Dikmans REGmg, et al. Quality of life and patient satisfaction after one-stage implant-based breast reconstruction with an acellular dermal matrix versus two-stage breast reconstruction (BRIOS): primary outcome of a randomised, controlled trial. *Lancet Oncol.* 2018 Sep;19(9):1205-14. doi: 10.1016/s1470-2045(18)30378-4. PMID: 30104147.
22. Potter S, Chambers A, Govindajulu S, et al. Early complications and implant loss in implant-based breast reconstruction with and without acellular dermal matrix (Tecnos Protexa(R)): a comparative study. *Eur J Surg Oncol.* 2015 Jan;41(1):113-9. doi: 10.1016/j.ejso.2013.08.016. PMID: 24011501.
23. Salzberg CA, Ashikari AY, Berry C, et al. Acellular Dermal Matrix-Assisted Direct-to-Implant Breast Reconstruction and Capsular Contracture: A 13-Year Experience. *Plast Reconstr Surg.* 2016 Aug;138(2):329-37. doi: 10.1097/prs.0000000000002331. PMID: 27064232.
24. Smith JM, Broyles JM, Guo Y, et al. Human acellular dermis increases surgical site infection and overall complication profile when compared with submuscular breast reconstruction: An updated meta-analysis incorporating new products(). *J Plast Reconstr Aesthet Surg.* 2018 Nov;71(11):1547-56. doi: 10.1016/j.bjps.2018.06.012. PMID: 30093286.
25. Santosa KB, Qi J, Kim HM, et al. Long-term Patient-Reported Outcomes in Postmastectomy Breast Reconstruction. *JAMA Surg.* 2018 Oct 1;153(10):891-9. doi: 10.1001/jamasurg.2018.1677. PMID: 29926096.
26. Jagsi R, Momoh AO, Qi J, et al. Impact of Radiotherapy on Complications and Patient-Reported Outcomes After Breast Reconstruction. *J Natl Cancer Inst.* 2018 Feb 1;110(2). doi: 10.1093/jnci/djx148. PMID: 28954300.
27. Pusic AL, Matros E, Fine N, et al. Patient-Reported Outcomes 1 Year After Immediate Breast Reconstruction: Results of the Mastectomy Reconstruction Outcomes Consortium Study. *J Clin Oncol.* 2017 Aug 1;35(22):2499-506. doi: 10.1200/jco.2016.69.9561. PMID: 28346808.
28. Higgins JP, Altman DG, Gotzsche PC, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *Bmj.* 2011 Oct 18;343:d5928. doi: 10.1136/bmj.d5928. PMID: 22008217.
29. Sterne JA, Hernan MA, Reeves BC, et al. ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions. *Bmj.* 2016 Oct 12;355:i4919. doi: 10.1136/bmj.i4919. PMID: 27733354.
30. National Heart, Lung, and Blood Institute. Study Quality Assessment Tools.; 2019. <https://www.nhlbi.nih.gov/health-topics/study-quality-assessment-tools>. Accessed on January 23, 2020.
31. Berkman ND, Lohr KN, Ansari M, et al. AHRQ Methods for Effective Health Care Grading the Strength of a Body of Evidence When Assessing Health Care Interventions for the Effective Health Care Program of the Agency for Healthcare Research and Quality: An Update. *Methods Guide for Effectiveness and Comparative Effectiveness Reviews.* Rockville (MD): Agency for Healthcare Research and Quality (US); 2008.
32. Berkman ND, Lohr KN, Ansari MT, et al. Grading the strength of a body of evidence when assessing health care interventions: an EPC update. *J Clin Epidemiol.* 2015 Nov;68(11):1312-24. doi: 10.1016/j.jclinepi.2014.11.023. PMID: 25721570.

33. Potter S, Davies C, Holcombe C, et al. International development and implementation of a core measurement set for research and audit studies in implant-based breast reconstruction: a study protocol. *BMJ Open*. 2020 Jan 20;10(1):e035505. doi: 10.1136/bmjopen-2019-035505. PMID: 31964677.
34. Potter S, Holcombe C, Ward JA, et al. Development of a core outcome set for research and audit studies in reconstructive breast surgery. *Br J Surg*. 2015 Oct;102(11):1360-71. doi: 10.1002/bjs.9883. PMID: 26179938.
35. Williamson PR, Altman DG, Blazeby JM, et al. Developing core outcome sets for clinical trials: issues to consider. *Trials*. 2012 Aug 6;13:132. doi: 10.1186/1745-6215-13-132. PMID: 22867278.
36. Guyatt GH, Oxman AD, Kunz R, et al. Going from evidence to recommendations. *Bmj*. 2008 May 10;336(7652):1049-51. doi: 10.1136/bmj.39493.646875.AE. PMID: 18467413.

VI. Abbreviations

ADM	acellular dermal matrix
AHRQ	Agency for Healthcare Research and Quality
AR	autologous reconstruction
ASPS	American Society of Plastic Surgeons
BIA-ALCL	breast implant-associated anaplastic large cell lymphoma
BMI	body mass index
DIEP	deep inferior epigastric perforator
EPC	Evidence-based Practice Center
FDA	Food and Drug Administration
GAP	gluteal artery perforator
IBR	implant-based reconstruction
KI	Key Informant
KQ	Key Question
LD	latissimus dorsi
NHLBI	National Heart, Lung, and Blood Institute
NMD	net mean difference
NRCS	nonrandomized comparative study
OR	odds ratio
PAP	profundal artery perforator
RCT	randomized controlled trial
ROBINS-I	Risk of Bias in Nonrandomized Studies of Interventions
SIEA	superficial inferior epigastric artery perforator
SoE	strength of evidence
SRDR-Plus	Systematic Review Data Repository-Plus
TEP	Technical Expert Panel
TMG	transverse musculocutaneous gracilis
TOO	Task Order Officer
TRAM	transverse rectus abdominis myocutaneous
TUG	transverse upper gracilis

VII. Summary of Protocol Amendments

If we need to amend this protocol, we will give the date of each amendment, describe the change and give the rationale in this section.

VIII. Review of Key Questions

AHRQ posted the Key Questions on the AHRQ Effective Health Care Website for public comment. The EPC refined and finalized them after reviewing of the public comments and seeking input from KIs. This input is intended to ensure that the Key Questions are specific and relevant.

IX. Key Informants (KIs)

We included a panel of KIs during Topic Refinement.

KIs are end users of research, including patients and caregivers, practicing clinicians, relevant professional and consumer organizations, purchasers of health care, and others with experience in making health care decisions. Within the EPC program, the KIs' role is to provide input into identifying and refining the Key Questions for research that will inform healthcare decisions. The EPC solicits input from KIs when developing questions for systematic review or when identifying high priority research gaps and needed new research. KIs are not involved in analyzing the evidence, writing the report, or reviewing the report, except as given the opportunity to do so through the peer or public review mechanism.

KIs must disclose any financial conflicts of interest greater than \$5,000 and any other relevant business or professional conflicts of interest. Because of their role as end-users, individuals are invited to serve as KIs and those who present with potential conflicts may be retained. The Task Order Officer (TOO) and the EPC work to balance, manage, or mitigate any potential conflicts of interest identified.

X. Technical Experts

Technical Experts constitute a multi-disciplinary group of clinical, content, and methodological experts who provide input in defining populations, interventions, comparisons, or outcomes and identify particular studies or databases to search. The Technical Expert Panel is selected to provide broad expertise and perspectives specific to the topic under development. Divergent and conflicting opinions are common and perceived as healthy scientific discourse that fosters a thoughtful, relevant systematic review. Therefore, study questions, design, and methodological approaches do not necessarily represent the views of individual technical and content experts. Technical Experts provide information to the EPC to identify literature search strategies and suggest approaches to specific issues, as requested by the EPC. Technical Experts do not do analysis of any kind; neither do they contribute to the writing of the report. They do not review the report, except as given the opportunity to do so through the peer or public review mechanism.

Members of the TEP must disclose any financial conflicts of interest greater than \$5,000 and any other relevant business or professional conflicts of interest. Because of their unique clinical or content expertise, individuals are invited to serve as Technical Experts and those who present with potential conflicts may be retained. The AHRQ TOO and the EPC work to balance, manage, or mitigate any potential conflicts of interest identified.

XI. Peer Reviewers

Peer reviewers are invited to provide written comments on the draft report based on their clinical, content, or methodological expertise. The EPC considers all peer review comments on the draft report in preparation of the final report. Peer reviewers do not participate in writing or editing of the final report or other products. The final report does not necessarily represent the views of individual reviewers. The EPC will complete a disposition of all peer review comments. The disposition of comments for systematic reviews and technical briefs will be published three months after the publication of the evidence report.

Potential Peer Reviewers must disclose any financial conflicts of interest greater than \$5,000 and any other relevant business or professional conflicts of interest. Invited Peer Reviewers may not have any financial conflict of interest greater than \$5,000. Peer reviewers who disclose potential business or professional conflicts of interest may submit comments on draft reports through the public comment mechanism.

XII. EPC Team Disclosures

EPC core team members must disclose any financial conflicts of interest greater than \$1,000 and any other relevant business or professional conflicts of interest. Related financial conflicts of interest that cumulatively total greater than \$1,000 will usually disqualify EPC core team investigators.

XIII. Role of the Funder

This project was funded under Contract No. HHS75Q80120D00001 (Task Order #01) from the Agency for Healthcare Research and Quality, U.S. Department of Health and Human Services. The TOO will review contract deliverables for adherence to contract requirements and quality. The authors of this report will be responsible for its content. Statements in the report should not be construed as endorsement by the Agency for Healthcare Research and Quality or the U.S. Department of Health and Human Services.

XIV. Registration

Once finalized, this protocol will be registered in the international prospective register of systematic reviews (PROSPERO).