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DEPARTMENT OF HEALTH AND HUMAN SERVICES

Agency for Healthcare Research and Quality

Supplemental Evidence and Data Request on Breast Reconstruction after Mastectomy

AGENCY: Agency for Healthcare Research and Quality (AHRQ), Health and Human Services (HHS).

ACTION: Request for supplemental evidence and data submissions.

SUMMARY: The Agency for Healthcare Research and Quality (AHRQ) is seeking scientific information submissions from the public. Scientific information is being solicited to inform our review on *Breast Reconstruction after Mastectomy,* which is currently being conducted by the AHRQ's Evidence-based Practice Centers (EPC) Program. Access to published and unpublished pertinent scientific information will improve the quality of this review.

DATES: *Submission Deadline* on or before 30 days after the date of publication of this Notice.

ADDRESSES:

E-mail submissions: epc@ahrq.hhs.gov

Print submissions:

Mailing Address:

Center for Evidence and Practice Improvement

Agency for Healthcare Research and Quality

ATTN: EPC SEADs Coordinator

5600 Fishers Lane

Mail Stop 06E53A

Rockville, MD 20857

Shipping Address (FedEx, UPS, etc.):

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5600 Fishers Lane

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FOR FURTHER INFORMATION CONTACT: Jenae Benns, Telephone: 301-427-1496 or Email: epc@ahrq.hhs.gov.

SUPPLEMENTARY INFORMATION: The Agency for Healthcare Research and Quality has commissioned the Evidence-based Practice Centers (EPC) Program to complete a review of the evidence for Breast Reconstruction after Mastectomy. AHRQ is conducting this systematic review pursuant to Section 902(a) of the Public Health Service Act, 42 U.S.C. 299a(a).

The EPC Program is dedicated to identifying as many studies as possible that are relevant to the questions for each of its reviews. In order to do so, we are supplementing the usual manual and electronic database searches of the literature by requesting information from the public (e.g., details of studies conducted). We are looking for studies that report on *Breast Reconstruction after Mastectomy*, including those that describe adverse events. The entire research protocol is available online at: https://effectivehealthcare.ahrq.gov/products/breast-reconstruction-mastectomy/protocol

This is to notify the public that the EPC Program would find the following information on *Breast Reconstruction after Mastectomy* helpful:

- A list of completed studies that your organization has sponsored for this indication. In the list, please *indicate whether results are available on ClinicalTrials.gov along with the ClinicalTrials.gov trial number*.
    - *For completed studies that do not have results on ClinicalTrials.gov*, a summary, including the following elements: study number, study period, design, methodology, indication and diagnosis, proper use instructions, inclusion and exclusion criteria, primary and secondary outcomes, baseline characteristics, number of patients screened /eligible /enrolled /lost to follow-up /withdrawn /analyzed, effectiveness/efficacy, and safety results.
- *A list of ongoing studies that your organization has sponsored for this indication*. In the list, please provide the ClinicalTrials.gov trial number or, if the trial is not registered, the protocol for the study including a study number, the study period, design, methodology, indication and diagnosis, proper use instructions, inclusion and exclusion criteria, and primary and secondary outcomes.
- Description of whether the above studies constitute *ALL Phase II and above clinical trials* sponsored by your organization for this indication and an index outlining the relevant information in each submitted file.

Your contribution is very beneficial to the Program. Materials submitted must be publicly available or able to be made public. Materials that are considered confidential; marketing materials; study types not included in the review; or information on indications not included in

the review cannot be used by the EPC Program. This is a voluntary request for information, and all costs for complying with this request must be borne by the submitter.

The draft of this review will be posted on AHRQ's EPC Program website and available for public comment for a period of four weeks. If you would like to be notified when the draft is posted, please sign up for the e-mail list at: https://www.effectivehealthcare.ahrq.gov/email-updates.

The systematic review will answer the following questions. This information is provided as background. AHRQ is not requesting that the public provide answers to these questions.

Key Questions (KQ)

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**

a) **chemotherapy** or

b) **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 ≥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)
    - Profundal 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

- 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≥10 per group
- Nonrandomized comparative studies (NRCSs), N≥30 per group
- Case-control studies, N≥100 per group
- Single group studies, N≥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 ≥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

- 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≥10 per group
- NRCSs, N≥30 per group
- Case-control studies, N≥100 per group
- Single group studies, N≥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 (≥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 ≥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

- 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≥10 per group
- NRCSs, N≥30 per group

- Case-control studies, N≥100 per group
- Single group studies, N≥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 (≥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 ≥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

- 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≥10 per group
- NRCSs, N≥30 per group
- Case-control studies, N≥100 per group
- Single group studies, N≥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 (≥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 ≥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

- 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 submusclar)
- 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≥10 per group
- NRCSs, N≥30 per group
- Case-control studies, N≥100 per group
- Single group studies, N≥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 (≥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 ≥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)
    - Profundal 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

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

Dated: June 26, 2020.

Virginia Mackay-Smith,

Associate Director.

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