Systematic review

Systematic review and critical appraisal of the impact of acellular dermal matrix use on the outcomes of implant-based breast reconstruction

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Background: **Acellular dermal matrix (ADM) may improve outcomes in implant-based breast reconstruction (IBBR). The aim of this study was critically to appraise and evaluate the current evidence for ADM-assisted IBBR.**

Methods: **Comprehensive electronic searches identified complete papers published in English between January 2000 and August 2013, reporting any outcome of ADM-assisted IBBR. All systematic reviews, randomized clinical trials (RCTs) and non-randomized studies (NRSs) with more than 20 ADM recipients were included. Studies were critically appraised using AMSTAR for systematic reviews, the Cochrane risk-of-bias tool for RCTs and its adaptation for NRSs. Characteristics and results of identified studies were summarized.**

Results: **A total of 69 papers (8 systematic reviews, 1 RCT, 40 comparative studies and 20 case series) were identified, all of which were considered at high risk of bias, mostly due to patient selection and selective outcome reporting. The median ADM group sample size was 51.0 (i.q.r. 33.0–127.0). Most studies were single-centre (54), and they were often single-surgeon (16). ADM was most commonly used for immediate (40) two-stage IBBR (36) using human ADM (47), with few studies evaluating ADM-assisted single-stage procedures (10). All reported clinical outcomes (for example implant loss) and more than half of the papers (33) assessed process outcomes, but few evaluated cosmesis (16) or patient-reported outcomes (10). Heterogeneity between study design and, especially, outcome measurement precluded meaningful data synthesis.**

Conclusion: **Current evidence for the value of ADMs in IBBR is limited. Use in practice should therefore be considered experimental, and evaluation within registries or well designed and conducted studies, ideally RCTs, is recommended to prevent widespread adoption of a potentially inferior intervention.**

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Introduction

Breast cancer affects over 50 000 women each year in the UK[1], of whom approximately 40 per cent[2] will require a mastectomy. The loss of a breast may impact profoundly on a woman's quality of life[3], and immediate breast reconstruction, reconstructive surgery performed at the same time as mastectomy, is offered routinely to all women unless contraindicated by co-morbidities or the need for adjuvant therapy, to improve outcomes[4]. Approximately one in five women requiring a mastectomy currently elects to undergo immediate breast reconstruction[5].

Implant-based breast reconstruction (IBBR) is the most commonly performed reconstructive procedure in the UK, accounting for almost 40 per cent of all immediate reconstructions performed after mastectomy for breast cancer[5,6]. Traditional subpectoral IBBR is usually performed as a two-stage procedure[7,8]. This is necessary because the subpectoral pocket created at the time of mastectomy is too small to accommodate a definitive implant and

insertion of a tissue-expander is required as a first stage. The expander is inflated gradually over a period of months until the pocket has been stretched to the desired size. The expander is then replaced by a definitive implant at a second operation. This process can produce good cosmetic results for women with small to medium-sized breasts, but is unsuitable for those whose breasts are large or ptotic[9]. The process of expansion is time-consuming for patients and professionals, and may be uncomfortable[10]. This approach commits women to a second procedure and hospital admission with the associated risks and financial implications.

The introduction of acellular dermal matrix (ADM) as an adjunct to IBBR may improve outcomes for women considering this procedure. The ADM, a sterile reconstructive tissue matrix from which the cells have been removed[11], is sutured between the lower border of the pectoralis muscle and the chest wall to create a lower-pole sling which augments the inferior aspect of the subpectoral pocket and provides inferolateral implant coverage (*Fig. 1*). This may facilitate greater initial intraoperative expander fill volumes and reduce the time to completion of expansion in two-stage expander–implant reconstruction, or allow a definitive implant to be inserted in a single-stage procedure with a fixed-volume implant without the need for tissue expansion[12–14]. It may also improve cosmetic outcomes by improving lower-pole projection and creating a more natural-looking ptotic result[13,15–21]. The single-stage ADM-assisted approach, compared with the two-stage expander–implant reconstruction with ADM commonly used in the USA, may offer maximal potential benefits to both patients and healthcare funders by improving outcomes and reducing treatment costs, and this procedure is currently favoured in the UK. There is a need, however, for this approach to be evaluated appropriately before any recommendations for widespread implementation into practice can be made.

The optimal method for evaluating new interventions in healthcare is to use well described and conducted randomized clinical trials (RCTs). It is recommended that novel interventions that are still developing be evaluated initially within prospective case series[22,23], and then in explanatory RCTs that can establish how and whether the intervention works under ideal conditions[24]. Finally, to inform health policy, multicentre large-scale pragmatic RCTs are recommended that are designed to establish whether the new intervention is superior to existing methods and associated with patient benefit[25]. The best evidence consists of meta-analyses and systematic reviews of existing data. Although these study designs are optimal, there is also a need to minimize bias within each study. Risk of bias can be assessed using validated and widely used instruments appropriate for each study design, including the Cochrane tool and its modifications for RCTs[26] and non-randomized

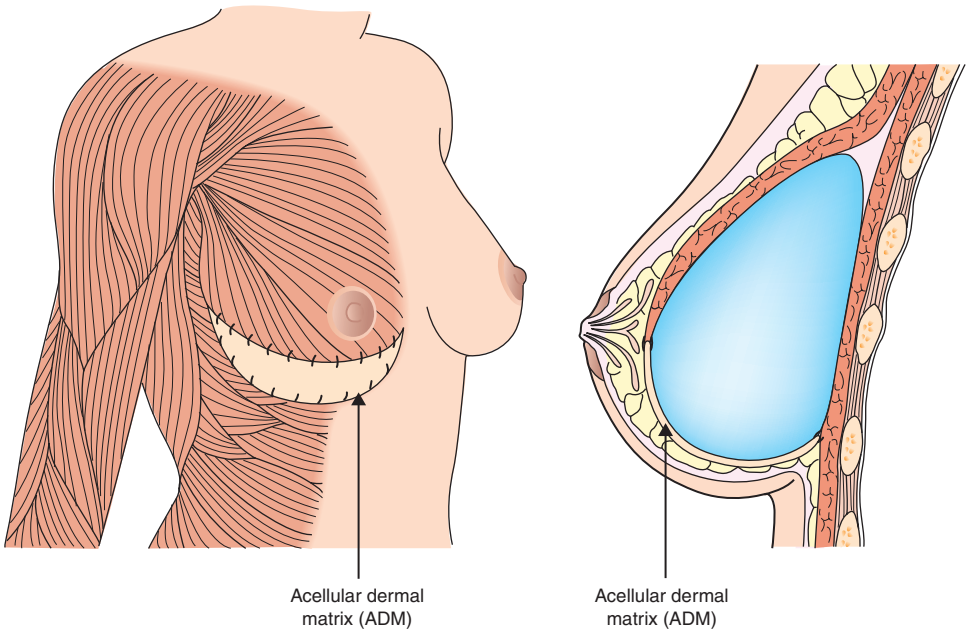

Fig. 1 Acellular dermal matrices (ADM) can be used to create a lower-pole sling, which augments the inferior aspect of the subpectoral pocket and provides inferolateral implant coverage. The ADM is sutured between the lower border of the pectoralis muscle and the chest wall

studies[27,28] respectively, and the AMSTAR (A MeaSurement Tool to Assess Systematic Reviews) checklist for systematic reviews[29–31].

The methodological quality of previously published evidence regarding the outcomes of ADM in IBBR has not been examined. The aim of the present systematic review was to evaluate critically the published literature reporting the clinical, patient-reported and cosmetic outcomes of ADM-assisted IBBR, and to summarize the best evidence with regard to the impact of ADM use on the outcomes of this form of reconstruction.

Methods

The protocol for this systematic review was registered in the PROSPERO international register of systematic reviews (reference number CRD42013005499) before data extraction was commenced.

Literature search strategy

The OvidSP versions of MEDLINE, Embase, Allied and Complementary Medicine (AMED), PsycINFO and Cochrane databases were searched using the keywords 'ADM', 'acellular derm$', 'Strattice', 'AlloDerm', 'SurgiMend', 'DermaMatrix' and 'Flex-HD', 'implant$', 'expander$', 'prosthe$' and 'breast$' (*Appendix S1*, supporting information).

The search was limited to human studies, published in English up to 1 August 2013. Studies published before January 2000 were excluded as they were unlikely to reflect current practice. Abstracts and conference reports were not included because of difficulties evaluating incomplete information.

Duplicate records were excluded, and the titles and abstracts of the remaining citations were screened independently for eligibility by two reviewers using predetermined selection criteria (*Appendix S2*, supporting information).

The reference lists of retrieved articles and identified reviews were searched manually to identify additional potentially relevant studies.

Selection of papers

Articles and systematic reviews reporting on the outcome of IBBR in women aged 18 years or over following a total mastectomy for breast cancer, preinvasive disease or risk reduction were eligible for inclusion. IBBR involving the use of expanders, expander–implants or fixed-volume implants as a single- or two-stage procedure in which ADM, irrespective of its manufacturer or biological origin, had been used were considered eligible. Articles and systematic reviews evaluating the use of ADM in chest wall reconstruction, mastopexy, volume replacement following breast conservation, revisional surgery or other reconstructive procedures not preceded by total mastectomy were excluded. All systematic reviews and RCTs, irrespective of sample size, were included, but non-randomized studies including fewer than 20 women in the ADM group were excluded as they were likely to reflect early case series that may have been influenced by the surgeons' learning curve[32].

Studies and systematic reviews were included if they had assessed one or more of the following four outcomes following IBBR with ADM. For the purpose of this study, the outcomes were defined as: clinical – any adverse event identified by a healthcare professional that occurred as a direct result of the reconstructive procedure whether or not additional interventions were required (such as implant loss, skin necrosis); patient-reported outcomes – any outcome derived directly from the patient without interpretation by an observer; cosmetic outcomes –any assessment of the appearance of the reconstructed breast, irrespective of how it was made; and process – any other potentially clinically relevant outcome related to the reconstruction process (such as initial fill volume) but not included in the above which may influence patient outcomes.

Papers were screened for inclusion independently by two reviewers using a standard pro forma of inclusion criteria (*Appendix S2*, supporting information). Uncertainties that remained after full-text review were resolved by discussion with an experienced methodologist. Reasons for exclusion were recorded.

Data extraction

Studies were classified by study design. Non-randomized studies were categorized as comparative studies if a direct comparison was made between patient groups, for example patients having IBBR with and without ADM, and as case series if no comparison was made.

For systematic reviews, data were extracted regarding: inclusion criteria for studies included in the review including type(s) of ADM, method of reconstruction (single- *versus* two-stage) and study design (RCTs or non-randomized studies); number of included studies; and outcomes assessed.

For primary studies, this included: study design; prospective or retrospective accrual of data; number of centres; number of surgeons performing reconstruction; type(s) of ADM used; type of prosthetic reconstruction (single-stage: fixed volume or adjustable expander/implant; two-stage; or

not stated); timing of reconstruction (immediate, delayed or not stated); sample size (number of patients with and without ADM, and total sample); and the types of outcome reported in the study (complications, patient-reported outcomes, cosmetic or process outcomes).

Standard pro formas were used for all data extraction (*Appendices S3* and *S4*, supporting information).

Critical appraisal

Systematic reviews and included studies were assessed for risk of bias using validated methodology.

Systematic reviews

Each systematic review was evaluated using AMSTAR, a validated checklist for assessing the methodological quality of systematic reviews[29–31]. AMSTAR consists of 11 items, including the assessment of: an *a priori* design; duplicate study selection and data extraction; comprehensiveness of the literature search; status of included publications; provision of a list of studies included and excluded from the review; provision of a description of the characteristics of included studies; evaluation of the scientific quality of included studies; appropriateness of conclusions of the review based on this assessment; appropriateness of methods used to combine study results; likelihood of publication bias; and inclusion of conflict of interest in both the review itself and included studies. Each item is assessed as 'yes', 'no', 'can't answer' or 'not applicable'. AMSTAR does not provide specific guidance on how to integrate answers to the 11 quality items into an overall judgement of the quality of the review. Therefore, in order to assign an overall judgement of quality for each review, interpretation of the AMSTAR tool was modified. A review was considered to be at low risk of bias, and thus of high methodological quality, if its conduct satisfied all of the following four key AMSTAR items: a comprehensive literature search was performed; the scientific quality of the included studies was assessed; these quality assessments were then used appropriately in formulating review conclusions; and the methods used to combine the findings were appropriate. If the review failed to meet one or more of these criteria, it was considered to be at high risk of bias.

Primary studies

Risk of bias in RCTs was assessed using the Cochrane risk-of-bias tool[26]. For non-randomized studies, the Cochrane tool was modified by omitting items regarding 'sequence generation' and 'allocation concealment', and replacing them with an assessment of whether clear inclusion and patient selection criteria were provided. All other items from the tool were applied to both RCTs and non-randomized studies. These included an assessment of: performance bias (participant blinding); detection bias (outcome assessor blinding); attrition bias (completeness of outcome data); and reporting bias (discrepancy of more than 1 in the number of outcomes described in the methods and reported in the results). Industry funding was considered to be a potential additional important factor, which is sometimes associated with bias[33], and was thus also evaluated for each study.

Two additional measures of study quality were assessed: evidence of peer review as a result of ethical or institutional review board approval; and the inclusion of a sample size calculation as an indication of sufficient study power.

Each of these factors was assessed by two reviewers and any discrepancies were resolved by discussion with the senior author.

Outcome reporting

For primary studies, additional data were extracted depending on the types of outcome assessed. For studies reporting surgical complications, a modified version of the Martin criteria[34,35] was used to evaluate the quality of outcome reporting. This included whether the study had reported: the total/overall rate of complications; the rate of procedure-specific complications; a definition of the complications assessed; complications graded by severity; whether the analysis was adjusted for risk factors such as smoking or radiotherapy; and the duration of follow-up. Any definitions provided were extracted and summarized.

Preliminary review of the identified studies suggested that patient-reported outcome assessment was limited and thus formal evaluation using the Efficace criteria[36] would be inappropriate. The types of patient-reported outcome assessed in each study and the instrument used (if stated) were therefore extracted and summarized. In the absence of consensus regarding the robustness of cosmetic outcome assessment in breast reconstruction[37], the method of cosmetic outcome assessment (photographs, clinical, patient self-report) used and whether the assessor was blinded to the use of ADM was evaluated and summarized. Finally, process outcomes assessed in each study were extracted and summarized. Each factor was assessed independently by two reviewers and discrepancies were resolved by discussion with the senior author.

Heterogeneity of identified studies and the appropriateness of data pooling were evaluated with members of the study team. Owing to an insufficient number of RCTs and the diversity of non-randomized evidence, statistical synthesis was deemed inappropriate. Descriptive information

regarding included studies was presented separately for each study design.

Results

Of the 307 abstracts identified from the electronic searches, 73 full papers were obtained for further assessment and, of these, 65 were retained. Three papers[15,18,38] were excluded on the basis of sample size and a further four were identified from the hand-search. A total of eight systematic reviews[39–46] and 61 primary papers were included in the review (*Fig. 2*).

The primary papers evaluated 12 973 ADM-assisted IBBRs in 10 260 women, and included one RCT[47] (36 reconstructions in 36 women), 40 comparative studies (11 224 reconstructions in 9152 women)[48–87] and 20 case series (1713 reconstructions in 1072 women)[12,13,16,17,19,21,88–101] (*Table 1*).

The eight systematic reviews included a median of 12 (range 8–48) studies, and predominantly considered the clinical outcomes of human ADMs. Six reviews[39–41,43,44,46] attempted to combine data in a meta-analysis to generate estimates of complication rates (*Table 2*).

The single randomized trial[47] was a multicentre study comparing immediate two-stage expander–implant reconstruction with and without AlloDerm®, and evaluated process, patient-reported and clinical outcomes (*Table 1*).

Of the 40 comparative studies, the majority were retrospective (37), single-centre (36) studies that reported the outcomes of two-stage expander–implant reconstruction with and without ADM (25). Nine studies[50–53,57,58,62,68,83] compared different types of ADM; three[57,84,87] specifically

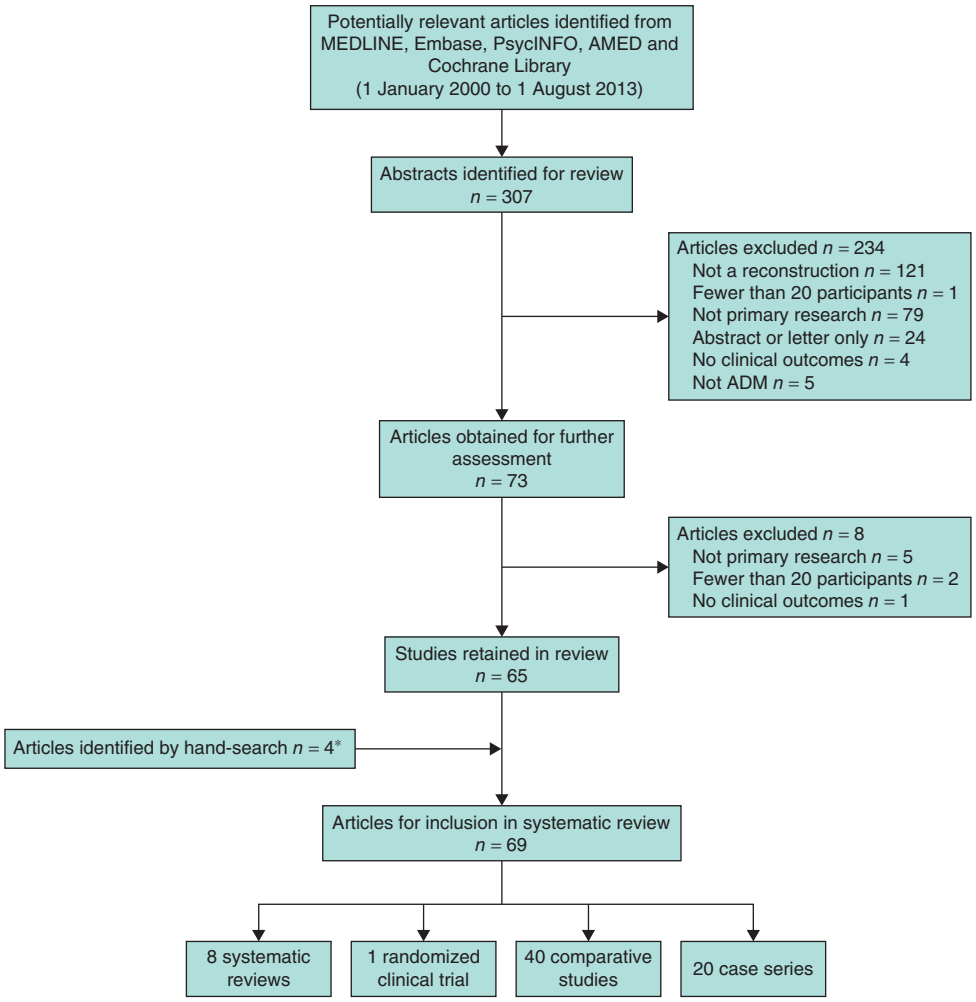

Fig. 2 PRISMA diagram for the systematic review. *From hand-search of 73 identified articles. ADM, acellular dermal matrix

Table 1 Demographics and outcome reporting of included primary studies by study design

		All studies ($n = 61$)	RCTs ($n = 1$)	Comparative studies ($n = 40$)	Case series ($n = 20$)
Study demographics					
Data collection	Prospective	7 (11)	1 (100)	3 (8)	3 (15)
	Retrospective	54 (89)	0 (0)	37 (93)	17 (85)
No. of centres	Single-centre	54 (89)	0 (0)	36 (90)	18 (90)
	Multicentre	7 (11)	1 (100)	4 (10)	2 (10)
No. of participating surgeons	Single surgeon	16 (26)	0 (0)	8 (20)	8 (40)
	Multiple surgeons	15 (25)	0 (0)	12 (30)	3 (15)
	Not stated	30 (49)	1 (100)	20 (50)	9 (45)
Type of ADM used	Human only	47 (77)	1 (100)	30 (75)	16 (80)
	Non-human (bovine/porcine) only	5 (8)	0 (0)	2 (5)	3 (15)
	Both human and non-human	3 (5)	0 (0)	3 (8)	0 (0)
	Not stated	6 (10)	0 (0)	5 (13)	1 (5)
Type of reconstruction§	Two-stage expander–implant	36 (59)	1 (100)	25 (63)	10 (50)
	Single-stage direct to implant	10 (16)	0 (0)	3 (8)	7 (35)
	Both	11 (18)	0 (0)	9 (23)	2 (10)
	Not stated	4 (7)	0 (0)	3 (8)	1 (5)
Timing of reconstruction	Immediate	40 (66)	1 (100)	25 (63)	14 (70)
	Immediate and delayed	10 (16)	0 (0)	9 (23)	1 (5)
	Not stated	11 (18)	0 (0)	6 (15)	5 (25)
Duration of follow-up reported		41 (67)	1 (100)	23 (58)	17 (85)
Reported length of follow-up (months)†		16.1 (9.6–21.6)	12.0 (12.0–12.0)	15.6 (8.7–23.2)	18.0 (10.0–19.2)
ADM sample size†¶		51.0 (33.0–127.0)	36.0 (36.0–36.0)	63.0 (36.0–192.0)	42.0 (26.0–59.5)
Total number of patients receiving ADM-assisted reconstruction		10 260	36	9152	1072
Total number of ADM-assisted breast reconstructions performed		12 973	36	11 224	1713
Clinical outcomes					
Studies reporting clinical outcomes of ADM-assisted reconstruction		61 (100)	1 (100)	40 (100)	20 (100)
Definitions of complications provided	No complications defined	25 (41)	0 (0)	11 (28)	14 (70)
	<25% of complications defined	17 (28)	1 (100)	12 (30)	4 (20)
	50% of complications defined	7 (11)	0 (0)	7 (18)	0 (0)
	>75% of complications defined	8 (13)	0 (0)	7 (18)	1 (5)
	All complications defined	4 (7)	0 (0)	3 (8)	1 (5)
Total complication rate reported		42 (69)	0 (0)	28 (70)	14 (70)
Reported total complication rate for ADM-assisted procedures (%)†		18.0 (12.1–29.3)	n.s.	21.9 (16.3–33.6)	9.3 (4.0–16.5)
At least one procedure-specific complication rate documented		61 (100)	1 (100)	40 (100)	20 (100)
No. of complications reported‡		5 (1–10)	4 (4–4)	5 (1–10)	5 (2–9)
Severity of complications graded		22 (36)	0 (0)	17 (43)	5 (25)
Risk factors accounted for in the analysis		42 (69)	0 (0)	33 (83)	9 (45)
Process outcomes					
No. of studies reporting process outcomes relating to use of ADM		33 (54)	1 (100)	21 (53)	11 (55)
PROs					
No. of studies reporting PROs		10 (16)	1 (100)	2 (5)	7 (35)
Method of assessment	Self-report validated questionnaires	4 (7)	1 (100)	1 (3)	2 (10)
	Not stated	6 (10)	0 (0)	1 (3)	5 (25)
Cosmetic outcomes					
No. of studies reporting cosmetic outcomes of ADM-assisted reconstruction		16 (26)	0 (0)	6 (15)	10 (50)
Outcome assessor	Patient only	5 (8)	0 (0)	1 (3)	4 (20)
	Healthcare professional(s) only	8 (13)	0 (0)	4 (10)	4 (20)
	Both patients and healthcare professionals	1 (2)	0 (0)	0 (0)	1 (5)
	Not stated/unclear	2 (3)	0 (0)	1 (3)	1 (5)
Assessment methods used	Panel photographic assessment	6 (10)	0 (0)	4 (10)	2 (10)
	3D photographic assessment	1 (2)	0 (0)	0 (0)	1 (5)
	Patient self-report questionnaires	4 (7)	0 (0)	1 (3)	3 (15)
	Not stated	5 (8)	0 (0)	1 (3)	4 (20)
Blinding of outcome assessor		4 (7)	0 (0)	4 (10)	0 (0)

Values in parentheses are percentages unless indicated otherwise; †values are median (i.q.r.) and ‡median (range). §Includes two studies using adjustable implants. ¶One study did not report the number of patients in each group, only the number of reconstructions. RCT, randomized clinical trial; ADM, acellular dermal matrix; n.s., not stated; PRO, patient-reported outcome; 3D, three-dimensional.

Table 2 Critical appraisal of systematic reviews and meta-analyses of the outcomes of acellular dermal matrix-assisted implant-based breast reconstruction

	Adetayo *et al.*[39] 2011	Ho *et al.*[40] 2012	Hoppe *et al.*[41] 2011	Jansen and Macadam[42] 2011	Kim *et al.*[43] 2012	Newman *et al.*[44] 2011	Nguyen *et al.*[45] 2011	Sbitany and Serletti[46] 2011
Demographics								
Type of ADM	A	A, F, S	A	A	H	H	H	A, S, F
Type of breast reconstruction	n.s.	n.s.	2-stage	1- and 2-stage	n.s.	IBR, 1- and 2-stage	n.s.	2-stage
No. of studies	Unclear†	16	8	14	48‡	12	12	9
Included study designs	NRS	NRS	Comparative studies only	NRS	NRS	NRS	NRS	NRS
Outcomes assessed	Clinical	Clinical	Clinical, process	Clinical	Clinical	Clinical	Clinical, process, cosmetic	Clinical
Critical appraisal								
A priori design	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
Duplicate study selection and data extraction	Yes	No	Data extraction only	Yes	Data extraction only	No	No	No
Adequate literature search*	Yes	Yes	Yes	Yes	Yes	No	No	Yes
Inclusion status not restricted by publication status	No	No (English papers only)	No (English, comparative studies)	Yes	No (English, studies with > 25 patients)	No (peer-reviewed published papers only)	No	No (English papers only)
Included and excluded studies listed	No (included studies only)	No (included studies only)	No (included studies only)	No (included studies only)	No (included studies only)	No (included studies only)	No	No (included studies only)
Characteristics of included studies provided	No	Yes	Yes	Yes	Yes	No	No	Yes
Scientific quality of included studies assessed*	No	Level of evidence but not risk of bias	'High-quality studies' but methods not stated	Level of evidence but not risk of bias	No	No	No	No
Conclusions appropriate based on scientific quality of included studies*	No	No	No	No	No	No	No	No
Appropriate methods used to combine individual study findings*	n.d.	n.d.	n.d.	No meta-analysis performed	n.d.	n.d.	No meta-analysis performed	n.d.
Likelihood of publication bias assessed	Yes	No	No	No	Yes	No	No	No
Conflict of interests included	No	No	No	No	No	No	No	No
Overall risk of bias of the review	High	High	High	High	High	High	High	High

*These four AMSTAR criteria were considered key criteria; a review had to fulfil all four to be considered at low risk of bias. If the review failed to meet any one or more of these criteria it was considered at high risk of bias. †Review evaluated breast and abdominal wall reconstructions; it was unclear how many papers evaluated breast reconstruction. ‡Six studies compared reconstruction with or without acellular dermal matrix (ADM) and there were 42 uncontrolled cohorts (13 with ADM alone and 29 submuscular only). A, AlloDerm® (LifeCell, Bridgewater, New Jersey, USA); F, FlexHD® (Ethicon, West Somerville, New Jersey, USA); S, Strattice™ (KCI, Gatwick, UK); H, human; n.s., not stated; IBR, immediate breast reconstruction; NRS, non-randomized studies; n.d., not able to be determined.

evaluated the impact of radiotherapy on ADM-assisted reconstruction, and five evaluated different aspects of the procedure including ADM size[54,55], antibiotic regimens[49], incision placement[79] and single- *versus* two-stage procedures[80]. The median sample size was 63 (i.q.r. 36–192). Three-quarters of studies (30) evaluated human ADMs only, and less than 60 per cent (23) reported the duration of follow-up.

The case series were most frequently single-centre (18) and often smaller (median sample size 42, i.q.r. 26–60) than comparative studies. These, however, were more likely than other study designs to report on the duration of follow-up (17), evaluate the outcomes of non-human ADMs (3), and consider patient-reported and cosmetic outcomes.

Critical appraisal

Systematic reviews

All systematic reviews were of low quality and at high risk of bias. Few (2 reviews) used predetermined quality criteria to select studies for inclusion (for example sample size[43] or study design[41]) or evaluated the quality of included studies (3)[40–42], and most included small case series (*Table 2*). Although six studies[39–41,43,44,46] conducted meta-analyses, the validity of pooling data from small non-randomized studies is questionable as the heterogeneity of included studies was often not assessed or reported with sufficient clarity for a judgement to be made[102].

Randomized trials

The single RCT[47] was well designed and at low risk of bias (*Table S1*, supporting information). This trial was stopped early by the Data Safety Monitoring Board owing to poor recruitment. The authors did not comment on reasons why this may have occurred, but at the time of the interim analysis only 65 patients (66 per cent of planned accrual) had been recruited over a 4-year period. The interim analysis was conducted using a sequential analysis methodology in order to evaluate the likelihood that the trial would yield a positive result (a significant benefit with ADM) if it achieved its planned accrual. This suggested that, based on the primary outcomes of postoperative pain and pain during the expansion period, the probability of achieving a positive result was 11 per cent and less than 1 per cent respectively, and the trial was stopped on this basis. The limited data were analysed and showed no differences in pain or physical well-being in the postoperative period ($P = 0.19$ and $P = 0.52$ respectively), during the expansion phase ($P = 0.65$ and $P = 0.77$) or before expander exchange ($P = 0.93$ and $P = 0.82$). The study was, however, underpowered and the results may have occurred by chance (*Table 3*).

Non-randomized studies

All 60 non-randomized studies were considered to be at high risk of bias. It was unclear how patients were selected for ADM *versus* standard submuscular procedures, with only one-third (22) reporting these details. Four[62,68,75,85] compared IBBR with and without ADMs conducted during consecutive time periods, three studies[66,67,71] used ADMs (or not) based on surgeons' preferences, three studies[12,59,76] reported that the decision to use ADM was made during surgery based on mastectomy skin-flap thickness, and one study[81] compared different surgeons' practices. These studies were therefore at high risk of selection bias and confounding, and the groups were not directly comparable. There was evidence of attrition bias in more than one-third of studies (21), and almost half (27) showed evidence of selective outcome reporting. Only half of the studies (30) had been subject to peer review by an ethics committee or institutional review board, and over one-third (24) were conducted by researchers who had financial associations with ADM manufacturers (*Table 3*; *Tables S2* and *S3*, supporting information).

Outcome reporting

Clinical outcomes

Some aspect of a clinical outcome was reported in all 61 primary studies, although two-thirds (42) documented only the total rate of complications in the study, making detailed understanding of outcomes impossible. There was a lack of consistency in the nature of complications evaluated. A total of 28 different complications were reported across the 61 studies, but no single complication was evaluated in all reports. The most commonly reported complications were infection (51 studies), seroma (44), mastectomy skin-flap necrosis (36), haematoma (32) and implant loss (32). Only 85 (27.3 per cent) of the 311 complications reported in the 61 papers were defined, and comparison of the definitions provided demonstrated marked heterogeneity in complication assessment between studies. Complications were graded in severity by about one-third of studies (22). Approximately two-thirds (42) of studies adjusted for risk factors in their analysis, but there was a lack of consistency in both the number and type of risk factors used. The risk factors adjusted for most commonly were radiotherapy (29 studies), body mass index (23) and smoking (20); others included age, initial expander fill volume, diabetes, type and timing of surgery and chemotherapy. Duration of follow-up was stated in 41 studies, but this was

Table 3 Critical appraisal of included studies by study design using the modified Cochrane risk-of-bias tool

	All studies (*n* = 61)	RCTs (*n* = 1)	Cohort studies (*n* = 40)	Case series (*n* = 20)
Selection bias assessment				
Adequate random sequence generation	1 (2)	1 (100)	n.a.	n.a.
Adequate allocation concealment	1 (2)	1 (100)	n.a.	n.a.
Clear inclusion/exclusion criteria or consecutive patients receiving procedure(s) included in study	48 (79)	1 (100)	33 (83)	14 (70)
Patient selection criteria for ADM procedures reported	22 (36)	n.a.	13 (33)	9 (45)
Performance bias assessment				
Participants blinded to allocation/treatment group				
Yes	1 (2)	1 (100)	0 (0)	0 (0)
No	60 (98)	0 (0)	40 (100)	20 (100)
Detection bias assessment				
Outcome assessors blinded to procedure performed				
Yes	8 (13)	1 (100)	5 (13)§	3 (15)
No	53 (87)	0 (0)	35 (88)	17 (85)
Attrition bias assessment				
Patient attrition accounted for				
Yes	39 (64)	1 (100)	26 (65)	12 (60)
No	22 (36)	0 (0)	14 (35)	8 (40)
Reporting bias				
Evidence of selective outcome reporting*				
Yes	28 (46)	1 (100)	12 (30)	15 (75)
No	33 (54)	0 (0)	28 (70)	5 (25)
Funding bias†	24 (39)	0 (0)	14 (35)	10 (50)
Other markers of study quality				
Evidence of peer review‡	30 (49)	1 (100)	23 (58)	6 (30)
Evidence of study power calculation	2 (3)	1 (100)¶	0 (0)	1 (5)

Values in parentheses are percentages. *Discrepancy of more than 1 in number of outcomes described in methods and reported in results. †Industry-funded or authors with financial interests or associations with acellular dermal matrix (ADM) manufacturers. ‡For example, institutional review board review or ethical approval. §Blinded cosmetic outcome assessment only. ¶Closed prematurely as failed to meet recruitment target. n.a., Not available.

limited with a median follow-up of 16.2 (i.q.r. 9.8–22.7) months across all studies.

Summary of clinical outcomes in comparative studies

The median complication rate following ADM-assisted IBBR was 18 (range 6–64) per cent, compared with 14 (5–45) per cent for standard two-stage expander–implant procedures (*Table S4*, supporting information). Of the 28 studies comparing IBBR with and without ADM, 12[48,56,58,66,67,70,73–75,77,78,86] suggested the complication rate to be higher in the ADM group; 12[51,52,59–61,63,64,69,71,72,81,82] suggested equivalence between ADM-assisted and standard procedures, and two[76,85] suggested that the complication rate may be lower when ADM was used. The remaining two studies[47,65] did not comment on comparative complication rates. Nine studies[50–53,57,58,62,68,83] compared different types of ADM. Although none of these identified any significant differences in complication rates between products, seroma rates were higher when AlloDerm® (LifeCell, Bridgewater, New Jersey, USA) was compared with Strattice™ (KCI, Gatwick, UK)[62], and when sterile was compared with aseptic AlloDerm®[52] (*Table S4*, supporting information).

Patient-reported outcomes

Patient-reported outcomes were reported in ten studies (1 RCT[47], 2 comparative studies[63,82] and 7 case series[13,17,21,90,91,93,100]). Seven studies[13,17,21,63,91,93,100] evaluated satisfaction with outcome; three[13,47,82] assessed pain, two[90,91] assessed cosmetic outcome and one[21] reported nipple sensation, but of these only four studies used a validated questionnaire (BREAST-Q in 1[47]; Breast Evaluation Questionnaire in 3[63,90,91]). Although the case series reported high levels of satisfaction and reduced pain with ADM-assisted reconstruction[13,17,21,90,91,93,100], the comparative studies failed to show a difference in patient satisfaction[63], postoperative pain[47,82] or physical well-being[47] between the ADM-assisted and standard implant-based reconstruction groups.

Cosmetic outcomes

There were 16 studies (6 comparative studies[55,63,72,80,85,87] and 10 case series[13,16,17,21,90–94,99]) that reported the cosmetic outcomes of ADM-assisted breast reconstruction. Cosmesis was assessed from photographs by a panel of assessors in six studies[16,72,80,85,87,99], using

self-report questionnaires in four studies[63,90,91,93] and three-dimensional photographic assessment in a single study[92]. Five studies[13,17,21,55,94] did not report how cosmesis was assessed. Of the three studies comparing IBBR with and without ADM, two[72,85] reported improved cosmetic outcome associated with ADM use as assessed by a blinded panel of assessors. The final study[63], however, failed to identify any differences in patient satisfaction between the two groups.

Process outcomes

Thirty-three studies (1 RCT[47], 21 comparative studies[50,54–56,58,59,61–63,65,67,68,75,78–83,85,86] and 11 case series[12,19,88–90,92,95,97–99,101]) reported a total of 26 different process-related outcomes. The most common were initial intraoperative expander fill volume (21), expander parameters such as size of prosthesis inserted (12), time to second stage (16) and number of expansions (14), but there was a lack of consistency in outcome selection between studies. There were 14 studies that compared expander dynamics in IBBR with and without ADM. Of these, nine studies[56,58,61,63,67,75,81,82,86] reported increased intraoperative expander fill volumes in the ADM group and four[58,63,81,82] reported that fewer fills were required to achieve the desired volume. Four studies[47,58,78,85] failed to demonstrate that ADM increased the rate of expansion or time to second stage compared with the standard approach.

The lack of consistency in both study design and outcome reporting was such that it was considered inappropriate to pool the data; thus a simple narrative summary of identified studies has been provided (*Tables S4* and *S5*, supporting information).

Discussion

There is currently a lack of high-quality evidence to demonstrate the impact of ADM use on the outcomes of IBBR. Existing studies are largely small retrospective and single-centre cohorts that are often at risk of bias, so that meaningful analyses of outcomes is not possible and published results reflect the views of the authors rather than reflecting data and evidence. The majority of studies report North American practice and have evaluated the use of human ADM in two-stage expander–implant reconstruction. Few have considered the outcomes of single-stage direct-to-implant procedures with xenogenic ADMs, as predominantly offered in the UK. Immunogenic differences between human and non-human products mean that it cannot be assumed that results from the US studies can be extrapolated[103]. Furthermore, although single-stage procedures may offer maximal benefits to both patients and healthcare providers by removing the need for a second operation, rigorous scientific evaluation is required before this approach can be recommended routinely. Ideally, well designed and conducted pragmatic multicentre RCTs are required to evaluate ADM and compare it with other forms of breast reconstruction. Trials in breast reconstruction, however, are challenging[104] and a more acceptable approach may be to support prospective implant registries, such as those used in orthopaedic surgery, thereby ensuring prospective follow-up and documentation of outcomes to prevent ineffective interventions being established.

Although a number of previous systematic reviews[39–46] have been undertaken, this is the first review critically to appraise the literature and review other reviews. Six[39–41,43,44,46] of the earlier reviews combined data from non-randomized studies to undertake meta-analyses but, given the heterogeneity of studies and outcomes demonstrated in this review, such an approach is largely inappropriate as studies are not directly comparable. Furthermore, most of the existing literature suffers from selection bias such that the outcomes of the individual studies cannot be relied upon. It is therefore not possible to draw any definitive conclusions regarding the impact of ADM use on the outcomes of IBBR from existing research, because of the heterogeneity of practice, outcome selection and the methodological weaknesses of the studies.

Although this systematic review critically evaluates the ADM literature, it has some methodological weaknesses. First, the review was limited to papers published in English. Potentially valuable and informative studies may therefore have been missed. Restricting the review to studies including more than 20 patients in the ADM group will have missed early case series[15,18,38]. These studies are unlikely to reflect the true outcomes of the established procedure as they will include ongoing refinements of the technique and the surgeons' learning curve, which has been clearly shown to impact adversely on the outcomes of ADM-assisted breast reconstruction[59]. Small studies are also likely to be less methodologically robust than the larger ones included in the present review. The possibility of publication bias cannot be excluded entirely as some of the research in this field is driven by the commercial sector. It is therefore possible that some of the commercially unfavourable research was suppressed. The present authors did not formally assess the likelihood of publication bias as there are no reliable methods by which this may be achieved, particularly in a review of this nature without statistical synthesis. The present search strategy was comprehensive and, despite the theoretical possibility of publication bias, it is unlikely that the existence of unpublished studies would have changed the conclusion of this review, that high-quality evidence to

support the use of ADM is lacking. The use of AMSTAR to evaluate systematic reviews of non-randomized studies is also atypical, as it was designed for systematic reviews of RCTs. Adaptation of AMSTAR for systematic reviews of non-randomized studies is currently under development (B. J. Shea, personal communication, 2014). Most of the relevant methodological features of systematic reviews included in AMSTAR are, however, relevant to all reviews of interventions, not just those including RCTs. Indeed, a recent study[105] that assessed the applicability and reliability of AMSTAR for assessment of systematic reviews of non-randomized studies demonstrated good psychometric properties, ease of use and high reliability, consistent with its application to systematic reviews of RCTs and supporting its use in this context.

Robust evaluation of novel interventions is essential[24], and well designed, pragmatic RCTs are required to evaluate definitively the impact of ADM on the outcomes of IBBR. The lack of relevant data relating to current practice and outcomes of ADM-assisted procedures in the UK, however, present particular challenges to the design and conduct of such a trial. There are insufficient data to inform the selection of appropriate comparators, outcomes, sample size or selection criteria. It is also unclear how many patients may be eligible to participate. The need for high-quality data regarding the outcomes of new approaches to implant-based breast reconstruction is recognized increasingly[14,103], but early progression to a poorly designed trial may alienate potential participants. Exploratory pretrial work is therefore essential and the implant Breast Reconstruction evaluation (iBRA) study (www.ibrastudy.com) is currently working with trainees in breast and plastic surgery to generate high-quality prospective outcome data to inform the design and conduct of a future trial. The trainee research collaborative model[106] has an excellent track record in the successful design and delivery of large-scale multicentre audit[107–110] and research projects[111,112], and it is anticipated that iBRA will be similarly successful with plans to recruit up to 1000 participants from 50 centres across the UK. This study will explore the practice and outcomes of implant-based breast reconstruction and allow the feasibility of a future trial to be determined effectively. Integrated methods to optimize recruitment will then be needed in the main trial to ensure that accrual targets are achieved by training and supporting surgeons who may be unfamiliar with recruiting patients to reconstruction trials[104,113].

If RCTs are not feasible, however, implant registries such as those used in orthopaedics may offer an alternative and acceptable means of ensuring the safety and effectiveness of ADMs and other implanted medical devices. Registries collect long-term outcome data and allow the early detection of adverse events, such as the high rate of revisional surgery detected in 2007 by the Australian National Joint Registry following articular surface replacement (ASR) and later by the British National Joint Registry which led to the withdrawal of the metal-on-metal ASR system[114]. The need for a registry was further highlighted by the recent Poly Implant Prosthèse (PIP) implant scandal[115–117], and moves to reinstate a breast implant registry in the UK are already in place through ICOBRA, the International Collaboration of Breast Registry Activities (www.plasticsurgery.org.au/protecting-patient-safety/icobra/), which is working to establish an internationally agreed and comparable minimum data set for breast implants and device registries. Extension of the scheme to include ADMs and other products may allow important long-term outcome data to be generated.

Despite the growing use of ADM in implant-based breast reconstruction, there is a lack of high-quality evidence to support the benefits of this form of reconstruction. Well designed RCTs that reflect UK practice are required for robust evaluation of ADM in breast reconstruction before its use can be recommended universally, and high-quality pretrial work is essential to determine the optimal design and conduct of these studies. Implant registries may also be necessary to allow the long-term outcomes of these products to be evaluated and safety assessed definitely.

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Supporting information

Additional supporting information may be found in the online version of this article:

Appendix S1 Search strategy (Word document)

Appendix S2 Items included in inclusion criteria pro forma (Word document)

Appendix S3 Data extraction pro forma for systematic reviews (Word document)

Appendix S4 Data extraction pro forma for individual studies (Word document)

Table S1 Critical appraisal of randomized clinical trials included in the systematic review (Word document)

Table S2 Critical appraisal of cohort studies included in the systematic review (Word document)

Table S3 Critical appraisal of case series included in the systematic review (Word document)

Table S4 Summary of clinical outcome papers included in the review: comparative studies (Word document)

Table S5 Summary of clinical outcome papers included in the review: case series (Word document)