



REVIEW ARTICLE

## A systematic review of randomised controlled trials in breast reconstruction

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### ABSTRACT

**Background:** For preference sensitive treatments, such as breast reconstructions, there are barriers to conducting randomised controlled trials (RCTs). The primary aims of this systematic review were to investigate what type of research questions are explored by RCTs in breast reconstruction, where have they been performed and where have they been published, and to thematise the research questions and thus create an overview of the state of the research field.

**Methods:** Randomised controlled trials investigating any aspect of breast reconstructions were included. The PubMed database was searched with a pre-defined search string. Inclusion and data abstraction was performed in a pre-defined standardised fashion. For the purpose of this study, we defined key issues as comparison of categories of breast reconstruction and comparison of immediate and delayed breast reconstruction, when the thematisation was done.

**Results:** A total of 419 abstracts were retrieved from the search. Of the 419, 310 were excluded as they were not RCTs concerning some aspect of breast reconstruction, which left us with 110 abstracts to be included in the study. The research questions of the included studies could more or less be divided into seven different themes inclusive of 2 key issues: Other issues – comparison of different categories of breast reconstruction, comparison of immediate and delayed breast reconstruction, surgical details within a category of breast reconstruction, surgical details valid for several categories of breast reconstruction, donor site management, anaesthetics, and non-surgical details. Only five studies compared key issues, and they all illustrate the challenges with RCTs in breast reconstruction.

**Conclusions:** A total of 110 publications based on RCTs in breast reconstruction have been published. Seven themes of research questions could be identified. Only five studies have explored the key issues. Better scientific evidence is needed for the key issues in breast reconstruction, for example by implementing a new study design in the field.

### ARTICLE HISTORY

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### KEYWORDS

Randomised controlled trial; breast reconstruction; research methodology; implant; free flap; diep flap; timing of surgery

### Background

Although breast reconstruction is an integral part of breast cancer treatment, there is little high-quality evidence for key issues such as which category of breast reconstruction and what timing is the most effective. Randomised controlled trials (RCT) are generally perceived as providing the highest level of scientific evidence for treatment effect [1, 2]. However, for preference sensitive treatments, such as breast reconstructions, there are barriers to conducting RCTs, which make both recruitment and achieving unbiased and generalisable results a challenge [3, 4]. Examples of barriers include that an RCT requires that there is solid uncertainty about which method achieves the best results. In the case of breast reconstruction, the operating surgeon must not prefer one method to another (*theoretical equipoise*) as this could result in both a biased recruitment as well as biased outcomes [3]. In addition, the patient must not have preformed ideas and clear preferences regarding the different methods (*principle of indifference*) based on, for example, other patients, patient organisations, and the media, as this also affects the recruitment and the results. Nonetheless, RCTs have been performed in breast

reconstruction. However, there is no current overview of what type of research questions have been examined with RCTs in breast reconstruction.

The primary aims of the study were to investigate what type of research questions RCTs in breast reconstruction explore, where they have been performed and where they have been published, and to thematise the research questions to create an overview of the state of the research field. The secondary aim was to investigate which RCTs examine the key issues, that is comparison of categories of breast reconstruction and immediate and delayed breast reconstruction. The studies examining key issues will be scrutinised regarding described barriers to conducting RCTs in breast reconstruction.

### Methods

#### Study design and pre-registration

This study adopted a systematic review methodology investigating which research questions have been studied in breast reconstruction.

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As the outcome is the nature of the research question and not the outcomes that are used in the individual studies, no risk of bias of individual evaluation was made. For the same reason, the study protocol was not pre-registered.

### Eligibility criteria and study selection

Randomised controlled trials investigating any aspect of breast reconstructions were included. All study designs that were not RCTs and all study protocols were excluded. The authors independently assessed whether the articles met the inclusion criteria and disagreements were resolved by discussion.

### Information sources and search strategy

The PubMed database was searched on 10 July 2023 for articles and abstracts, without time limit. The search was limited to RCTs published in English, French, Italian, Swedish, Danish, and Norwegian. The search string was ((breast) AND (reconstruction)). The full-text article was read when eligibility for inclusion could not be assessed by reading the abstract. Disagreements were resolved by discussion.

### Data abstraction

For all studies comparators, year of publication, journal, and study country were collected. For studies comparing different categories of techniques for breast reconstruction information collected included: first author, year of publication, comparators, study design, primary outcome, sample size calculation, did eligible patients asked for inclusion, randomised patients, number of randomised patients that did not receive allocated treatment, number of patients who discontinued treatment, number of patients analysed for the primary outcome, and conclusions of the study.

### Definitions

For the purpose of this study, we defined key issues as comparison of categories of breast reconstruction and comparison of immediate and delayed breast reconstruction. A category of reconstruction is a principal technique, such as autologous reconstruction and implant-based reconstruction. An immediate breast reconstruction is performed at the same time as the mastectomy whereas a delayed reconstruction is performed later, in a separate operation.

### Results

A total of 419 abstracts were retrieved from the search. Out of these, 309 abstracts were excluded as they were not RCTs concerning some aspect of breast reconstruction, which left us with 110 abstracts to be included in the study (Figure 1, Table 1). There were no disagreements regarding eligibility for inclusion and data selection. The first RCT in breast reconstruction was published in 1983 [5], and the annual number of publications has been increasing since 2013 (Figure 2). Randomised controlled trials in breast reconstruction have most frequently been published in Plastic and Reconstructive Surgery, Journal of Plastic Reconstructive and Aesthetic Surgery/British Journal of Plastic Surgery, Annals of Plastic Surgery, and Journal of Plastic Surgery and Hand Surgery/Scandinavian Journal of Plastic and Reconstructive Surgery and Hand Surgery (Table 1). The research questions of the included studies could more or less be divided into seven different themes of which two represent key issues in breast

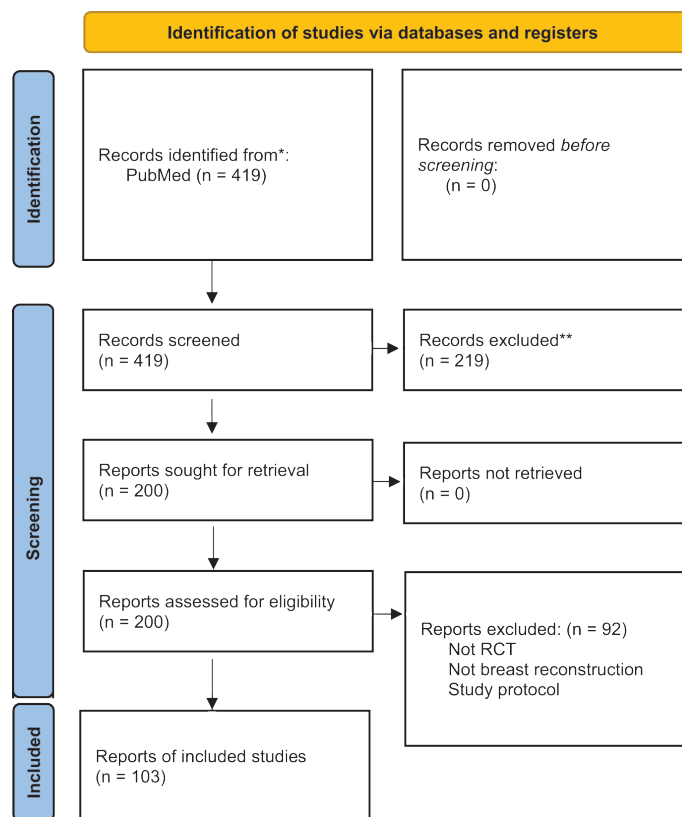
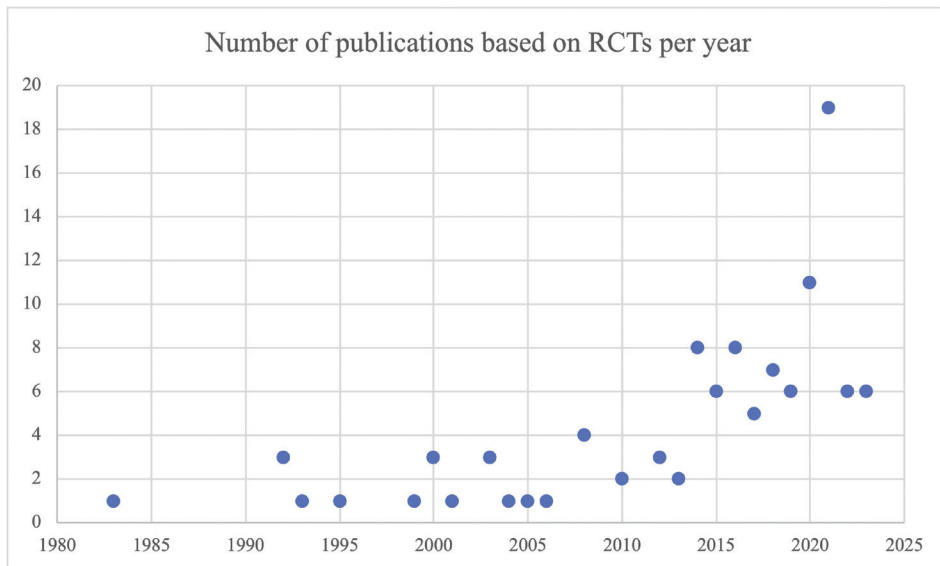


Figure 1. PRISMA diagram.

Table 1. Publications per journal.

Journal	Number of publications
Plastic and Reconstructive Surgery	30
Journal of Plastic Reconstructive and Aesthetic Surgery/	17
British Journal of Plastic Surgery	
Annals of Plastic Surgery	11
Journal of Plastic Surgery and Hand Surgery/	7
Scandinavian Journal of Plastic and Reconstructive	
Surgery and Hand Surgery	
British Journal of Surgery	6
Trials	3
Aesthetic Surgery Journal	2
Aesthetic Plastic Surgery	2
Annals of Surgery	2
Annals of Surgical Oncology	2
Breast Cancer Research and Treatment	2
European Journal of Surgical Oncology	2
JAMA Network Open	2
Lancet Oncology	2
Lancet	1
BJS Open	1
BMC Medical Informatics and Decision Making	1
Clinical Breast Cancer	1
Clinical Hemorheology and Microcirculation	1
Current Oncology	1
European Journal of Anaesthesiology	1
European Journal of Oncology Nursing	1
Journal of American College of Surgeons	1
Journal of Investigative Surgery	1
Journal of Reconstructive Microsurgery	1
Journal of Surgical Oncology	1
Journal of Tissue Viability	1
JAMA Surgery	1
JMIR mHealth and uHealth	1
PLoS One	1
Regional Anesthesia & Pain Medicine	1
Supportive Care Cancer	1
World Journal of Surgical Oncology	1



**Figure 2.** Number of publications per year. Search performed in PubMed 10.07.2023.

reconstruction: comparison of different categories of breast reconstruction (key issue), comparison of immediate and delayed breast reconstruction (key issue), surgical details within a category of breast reconstruction, surgical details valid for several categories of breast reconstruction, donor site management, anaesthetics, and non-surgical details (Table 2).

Only five studies compared key issues in breast reconstruction, that is compared different categories of breast reconstruction and delayed and immediate breast reconstruction head-to-head (Table 3). These five studies were all conducted in Europe. The study comparing immediate and delayed breast reconstruction was conducted in 1983 when breast reconstruction was much less common than it is today. Four studies compared different categories of breast reconstruction techniques head-to-head (Table 3), one Dutch [6] and three Swedish, from three different centres [7–11].

All five studies illustrate the challenges with RCTs in breast reconstruction (Table 2). In four of the studies [7, 8, 11, 12], a substantial part of the eligible patients (25% [30/121], 38% [54/141], 41% [51/125], and 43% [172/405], respectively) declined participation in the study, most frequently because they had a preferences for a particular reconstructive technique [7, 12]. Some participants dropped-out of the studies after randomisation, most commonly because they did not want the procedure that they had been randomised, 18% (16/91) and 19% (18/93), respectively [6, 12]. In one of studies [11], a total of 13% (31/233) of the participants, were excluded after randomisation both due to patients' and surgeons' preferences.

## Discussion

This is a systematic review examining what research questions in breast reconstruction have been studied in RCTs. The review identifies seven themes of research questions. Most of the studies compare details within one category of breast reconstruction (Table 1); only four studies compare different categories of breast reconstruction head-to-head, and one compares immediate versus delayed breast reconstruction (Table 1).

Previous studies have revealed that some surgeons are of the view that trials in breast reconstruction are no longer necessary as "things have moved on a bit in breast reconstruction" [13]. This is clearly contradicted by the findings of the present review as only five RCTs address the key issues such as comparison of different categories of





breast reconstruction and of immediate and delayed breast reconstruction. The clinical choice between immediate and delayed breast reconstruction still seems to be based on surgeons' personal beliefs and assumptions rather than on scientific evidence [14–16], and a clear superiority regarding patient reported outcomes has not been shown in studies and audits [16, 17]. Our review indicates that the research field of breast reconstruction might still be quite immature in terms of high-quality evidence for key issues.

Regarding barriers to RCTs in breast reconstruction, surgeons' equipoise seems to be central [3]. Qualitative studies [3, 13] have demonstrated that surgeons often believe that randomisation is not acceptable in breast reconstruction, especially not between different categories of breast reconstruction; although, their opinionated views seems to be driven by their own personal strong preferences rather than objective reasons [13]. One opinion that is often put forward, is that the surgeons know which method is appropriate for a certain patient [13]. The barrier to randomise between different categories of breast reconstruction is clearly reflected in the research questions that have been investigated in RCTs, found in the present review. We agree that there are patients that are unsuitable or particularly suitable for certain categories of breast reconstruction. However, these are not the patients for which a scientific evidence base for choice of category is necessary. The great majority of patients are equally suitable for several categories of breast reconstruction and this is the group that must be studied to create evidence-based guidelines. We propose that this issue is resolved by rigorous inclusion and exclusion criteria when future RCTs are designed, so that only patients eligible for all studied categories of breast reconstruction are included.


In recent years, there are indications that the choice of category of breast reconstruction has been increasingly affected by professional conflicts and the individual surgeon's competence [18]. In some units, general surgeons specialised in breast surgery, with skills mainly in implant-based breast reconstruction (IBR), have assumed responsibility for IBR and the primary discussion regarding breast reconstruction which could infer a risk that only patients actively requesting autologous breast reconstruction, or considered unsuitable for IBR by the surgeon, are referred to a plastic surgeon [19–22]. Hence, there could be strong incentive for both surgeons and plastic surgeons to promote "their" category of breast reconstruction. Such professional conflicts should not be allowed to impede high quality studies.

[AQ9] **Table 2.** Research questions/comparators in RCTs in breast reconstruction and their themes.

**Key issue: Comparison of different categories of breast reconstruction**







- Autologous fat transfer versus implant-based breast reconstruction in non-radiated patients [6] 
- LTD versus LD versus TRAM (SVEA) [7, 8] 
- DIEP versus LD in radiated patients and tissue expander + implant versus thoracodorsal flap and implant in non-radiated patients (GoBreast) [10, 11] 
- DIEP versus . implant based breast reconstruction in non-radiated patients [9, 12] 

**Key issue: Comparison of immediate and delayed breast reconstruction**




- Immediate versus delayed breast reconstruction [5] 

**Surgical details within a category of breast reconstruction**




**Implant-based breast reconstruction**

- Different types of implants/tissue expanders [31–34] 
- ADM versus no ADM [35–41] 
- Different types of ADMs and meshes [11, 42–48] 
- Fast versus slow tissue expansion [49–52] 
- One versus two stages [53–55] 
- Fat transfer/Lipofilling as an adjunct [56] 

**Autologous breast reconstruction**

- Preoperative imaging versus no preoperative imaging and different types of preoperative imaging [57–60] 
- Different regimes for pedicle length [61] 
- Internal mammary vessels versus thoracodorsal vessels as recipient vessels [62] 

**Pedicled flaps**

- Type and timing of LD flap [4] 
- Denervation versus no denervation of LD [63] 
- LD-flap versus TAP-flap (that is a back flap, based on thoracodorsal vessels/ perforators for thoracodorsal vessels, with or without muscle) [64, 65] 






**Surgical details valid for several categories of breast reconstruction**

- Different techniques for dissection /electrocautery [66–68] 
- Different techniques for fat transfer [69] 











**Donor site management**

- Different regimes for abdominal closure after abdominally based flap [70–77] 
- Different regimes for back closure after latissimus dorsi harvest [78–82] 

**Anaesthetics**




- Regimes for pain control [83–96] 
- Regimes for PONV prophylaxis [97] 
- Vasopressor versus fluid administration [98] 
- Sevoflurane preconditioning versus no sevoflurane [99] 
- Different regimes for perfusion promoting drugs [100, 101] 

**Non-surgical details**



- Drain usage [102, 103] 
- Seroma treatment [104] 
- Antibiotics [105–107] 
- Dressings and bras [108–112] 
- Wound care [113] 
- Surgical draping [114] 
- Physiotherapy [115, 116] 
- Alternative medicine as an adjunct [117] 
- Different drugs to prevent capsular contracture [118, 119] 
- Preoperative information and decision aids [120–130] 

ADM: acellular dermal matrix; AFT: autologous fat transfer/lipofilling; DIEP: deep inferior epigastric perforator flap; IBR: implant-based breast reconstruction; LD: latissimus dorsi flap; LTD: Lateral thoracodorsal flap; NR: not reported; PONV: postoperative nausea and vomiting; TAP: thoracodorsal artery perforator flap; TRAM: transverse rectus abdominis myocutaneous flap.

**Table 3.** RCTs comparing different categories of breast reconstruction.

Author, country, year, study name	Comparators	Study design	Primary outcome	Sample size calculation	Randomization period	Eligible patients asked for inclusion	Randomized	Did not receive allocated treatment	Discontinued treatment due to patient factors	Analysed for primary outcome	Conclusions
<b>Key issue: comparison of different categories of breast reconstruction</b>											
Brandberg, 1999–2000, Stockholm, SVEA [7, 8] 	LTD versus LD versus pedicled TRAM	RCT with active controls Stratified into Group A: All alternatives Group B: LD vs TRAM	Questionnaires	NR	1994–1996	141 “The most common reasons for nonparticipation were requests for autogenous tissue or the simplest operation possible.”	87 LTD 16 LD:30 TRAM: 29 NR:12	12 (1 death, 1 recurrence, 10 “practical reasons”)	NR	61	“that breast reconstruction is a valuable tool for the mastectomised patient to cope with her problems in everyday life and that significant positive changes in quality of life may follow” “only minor differences between the three methods”
Brorson, Gothenburg, Sweden, GoBreast [10, 11] 	DIET- versus LD in radiated patients and IBR versus LTD + implant in non-radiated patients	RCT with an active control 1:1 allocation Single centre 12 months follow-up	Complications	Based on aesthetic outcome	2008–2015	405 Declined participation: 172	233 Radiated arm: DIEP 44 LD 39 Non-radiated arm: IBR: 9 LTD: 13 Recurrences/other cancer: 9 Mutation carriers: 2	Changed their minds after randomisation DIEP:4 LD:5 IBR: 9 LTD: 13 Recurrences/other cancer: 9 Mutation carriers: 2	0	DIET 34 LD 32 IBR 70 TD 55	Complication frequencies were similar for both methods in each arm bit the complication profile varied
Piatkowski, 2023, the Netherlands [6] 	Lipofilling AFT versus IBR in non-radiated patients	RCT with an active control 1:1 allocation ratio Multicentre-conducted in 7 hospitals. 12 months follow-up	QoL	Standardized effect size expressed as Cohen <i>d</i> of 0.50 2-tailed $\alpha$ 0.05, Power 80%. Dropout rate: 15% 101 patients per group	2015–2019	193	191 IBR 93 AFT 98	AFT: 2 changed their mind IBR: 18 because they did not want implants	AFT: treatment too heavy	AFT: 64 IBR: 68	AFT group has a higher QoL

**Table 3.** (Continued)

Author, country, year, study name	Comparators	Study design	Primary outcome	Sample size calculation	Randomization period	Eligible patients asked for inclusion	Randomized	Did not receive allocated treatment	Discontinued treatment due to patient factors	Analysed for primary outcome	Conclusions
Tallroth, Malmö, Sweden [9, 12] 	DIET versus IBR ("standard treatment") in non-radiated patients	RCT with an active control 1:1 allocation ratio Single-centre Mean follow-up 63 months	QoL Costs	NR	2012–2018	121 28 did not want a DIEP 1 did not want an abdominal scar 1 wanted a reconstruction asap	91 40 IBR 50 DIEP	IBR: 10 4 withdrew as they wanted a DIEP 3 did not want reconstruction 1 did not meet weight criteria 1 recurrence 1 chose other hospital IBR: 6 3 withdrew as they wanted IBR 2 did not want reconstruction 1 did not meet weight criteria	NR	IBR: 29 DIEP: 44	Patients reconstructed with DIEP are more satisfied with their breasts DIEP requires more resources, has a higher complication rate, and cost more during the first 30 days.
<b>Key issue: Comparison of immediate and delayed breast reconstruction</b>											
Dean, 1983, UK [5] 	Immediate versus delayed breast reconstruction	RCT with controls (Unclear if the women had had delayed breast reconstruction when evaluated)	Psychiatric interview and questionnaires	NR	1978–1980	125 51 were not interested in breast reconstruction. 7 wanted an immediate breast reconstruction	64 33 immediate BR 31 mastectomy alone	0	0	50	"Immediate breast reconstruction reduced the psychiatric morbidity assessed 3 months after operation, predominantly in women with unsatisfactory marriages. Women who underwent reconstruction had more freedom of dress and were less likely to be repulsed by their own naked appearance than women who did not undergo reconstruction. Sexual and social morbidity were not affected"

The *principle of indifference* [23] is also an important factor in RCTs. It entails that the patients must not have pre-formed ideas and clear preferences regarding the different methods compared in the RCT. When it comes to breast reconstruction, this is impossible to achieve as most patients retrieve information about breast reconstruction from a myriad of sources, for example patient organisations and the media [4, 24]. Treatments, such as breast reconstruction, which are performed mainly to increase quality of life are particularly prone to patients' preferences and pre-formed conceptions and studies have suggested that the freedom of choice regarding reconstruction versus no reconstruction and category of breast reconstruction itself has an effect on the outcome of the procedure [25]. Hence, patients' preferences are a factor that cannot be disregarded when RCTs are designed in breast reconstructions. The RCTs comparing different categories of breast reconstruction, included in the present review, clearly showed that patients' preferences affected both recruitment and drop-outs (Table 3). For example, in Sweden standard treatment is IBR in patients who have not had radiotherapy and autologous in patients who have radiotherapy [26], and therefore in the RCT comparing implant-based reconstruction and deep inferior epigastric perforator flap (DIEP) in non-radiated patients, offered the patients the possibility of a DIEP which normally is accessible only for radiated patients. As a consequence, the *external validity* of the study might have been affected, as only patients who prefer autologous reconstruction were likely to accept randomisation [12] and the results therefore are not generalisable to the clinical population. Patients' preferences could also reduce *internal validity* as randomisation to the (non-) preferred strategy could affect both adherence to the protocol (*reluctant acquiescence phenomenon*) and outcome measurements [10]. Moreover, the concept of randomising patients to different categories of reconstruction might contradict the spirit of patient-centred care [27]. In summary, patients' preferences might make a traditional RCT an inappropriate study design to investigate key issues, which requires novelty when the studies are designed.

An approach to diminish the effect of patients' preferences, facilitate recruitment, increase patient centricity, decrease the risk of excluding large patient groups, and make the results more generalisable to the clinical population, when preference sensitive interventions are compared, is as a partially randomised patient preference trial (RPPT) design methodology [28]. In an RPPT, patients with a clear preference are treated accordingly and patients without a distinct preference are randomised in the traditional way. The RPPT design provides data on both external and internal validity [28], enables a more efficient inclusion of participants, and a clinically more representative population, while maintaining a high external and internal validity [28]. In addition, the RPPT design is a methodology that would allow for shared decision making, which is an important factor in breast reconstruction [29, 30]. Hence, the RPPT design could be one methodology to explore and develop for studies in breast reconstruction.

This review has some inherent weaknesses as the search was made limiting the results to studies classified as RCTs in PubMed. Hence, there is a risk that misclassification in PubMed or a lack of indexation in PubMed may have affected the results. Moreover, before the CONSORT guidelines for reporting, the declaration of RCTs was less clear which might also have affected the results of the present study. In addition, we have counted the number of publications and not the number of RCTs. There might be multiple publications stemming from one RCT.

In conclusion, 110 publications based on RCTs in breast reconstruction have been published. Seven themes of research questions of RCTs in breast reconstruction could be identified:

- Key issue – comparison of different categories of breast reconstruction
- Key issue – comparison of immediate and delayed breast reconstruction
- Surgical details within a category of breast reconstruction
- Surgical details valid for several categories of breast reconstruction
- Donor site management
- Anaesthetics
- Non-surgical details.

Only five studies have explored key issues. Better scientific evidence is needed for the key issues in breast reconstruction. One way to achieve this could be to implement new study designs in the field.

## Statements and declarations

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## Disclosure statement

The authors declare that they have no competing interests.

## Authors' contributions

EH and AP made the searches and analysed and interpreted the data. EH wrote the first manuscript draft. AP, EWJ, CL, AU, and KS revised the manuscript. All authors read and approved the final manuscript.

## Ethics approval and consent to participate

This is a systematic review of previously published studies and hence no ethics approval is necessary.

## Consent for publication

NA.

## Availability of data and materials

All data generated or analysed during this study are included in this published article.

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