

# A systematic methodological review of reported perioperative variables, postoperative outcomes and hernia recurrence from randomised controlled trials of elective ventral hernia repair

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# Hernia

## A Systematic Methodological Review of Reported Perioperative Variables, Postoperative Outcomes and Hernia Recurrence from Randomised Controlled Trials of Elective Ventral Hernia Repair: Clear Definitions and Standardised Datasets are needed.

--Manuscript Draft--

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<b>Abstract:</b>	<p><b>Background</b> This systematic review assesses the perioperative variables and post-operative outcomes reported by randomised controlled trials (RCTs) of ventral hernia repair. This review focuses particularly on definitions of hernia recurrence and techniques used for detection.</p> <p><b>Objective</b> Our aim is to identify and quantify inconsistency in perioperative variable and postoperative outcome reporting so as to justify future development of clear definitions of hernia recurrence and a standardised dataset of such variables.</p> <p><b>Methods</b> The PubMed database was searched for elective ventral hernia repair RCTs reported January 1995 to March 2016 inclusive. Three independent reviewers performed article screening, and two reviewers independently extracted data. Hernia recurrence, recurrence rate, timing and definitions of recurrence, and techniques used to detect</p>	

	<p>recurrence were extracted. We also assessed reported post-operative complications, standardised operative outcomes, patient reported outcomes, pre-operative CT scan hernia dimensions, intra-operative variables, patient co-morbidity, and hernia morphology.</p> <p><b>Results</b> 31 RCTs (3367 patients) were identified. Only 6 (19.3%) defined hernia recurrence and methods to detect recurrence were inconsistent. Sixty-four different clinical outcomes were reported across the RCTs, with wound infection (30 trials, 96.7%), hernia recurrence (30, 96.7%), seroma (29, 93.5%), length of hospital stay (22, 71%) and haematoma (21, 67.7%) reported most frequently. Fourteen (45%), 11 (35%) and 0 trials reported CT measurements of hernia defect area, width and loss of domain respectively. No trial graded hernias using generally accepted scales.</p> <p><b>Conclusion</b> Ventral hernia RCTs report peri- and post-operative variables inconsistently, and with poor definitions. A standardised minimum dataset, including definitions of recurrence, is required.</p>
<p><b>Response to Reviewers:</b></p>	<p>Reviewers' comments:</p> <p>1)</p> <p>Reviewer #1: - Authors answer: "We believe the Reviewer is incorrect. The PRISMA guideline stipulates at least ONE database. In our prior experience (two of the authors - SH and SM - have longstanding, extensive prior experience of systematic review and meta-analysis); there is little additional gain beyond PUBMED (e.g. EMBASE, COCHRANE) when the topic of interest is clearly clinical research, as is the case here"</p> <p>Reviewer comment: In paper methods the authors wrote: "This systematic review was reported in line with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement[25]. Reference 25 is: "Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gøtzsche PC, Ioannidis JPA, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. J Clin Epidemiol. 2009;62(10):e1-34."</p> <p>In the PRISMA statement in point 3 (development of PRISMA) you can read "The PRISMA Statement was developed by a group of 29 review authors, methodologists, clinicians, medical editors, and consumers". Furthermore, PRISMA authors continue to write in point 6 (The PRISMA checklist) item 7 (Information sources) "The National Library of Medicine's MEDLINE database is one of the most comprehensive sources of health care information in the world. Like any database, however, its coverage is not complete and varies according to the field. Retrieval from any single database, even by an experienced searcher, may be imperfect..."</p> <p>As noted in the first review the access to a single database when performing a systematic review is an important methodological flaw and against the recommendations of PRISMA statement.</p> <p>RESPONSE#1: The same publication contains a checklist and under the heading Search (point number 8 of the checklist) it reads: 'Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.' We have therefore adhered to PRISMA guidelines. Again, we wish to return to the point made by us originally that the PUBMED search engine is likely to identify the large majority of indexed research dealing with this topic. We identified 31 RCTs and believe strongly that our conclusions would not change materially even if we were able to identify a small amount of further research by searching another database. Many systematic reviews of clinical research limit themselves to PUBMED. In addition, for our search we extensively reviewed PUBMED and we identified and examined 6.5K abstracts!</p> <p>2)</p> <p>- Authors answer: "As for all of our research projects, we do have a protocol. As per usual practice, this has not been subject to peer-reviewed publication but we would be happy to let the Editor have sight of this should he feel it necessary. The research has been registered with the appropriate registry. PROSPERO 2016: CRD42016043071."</p>

Reviewer comment: After look through CRD42016043071 in PROSPERO web (<https://www.crd.york.ac.uk/prospéro/>) the document entitled "Protocol for a systematic review of abdominal wall reconstruction: what perioperative parameters predict successful ventral hernia repair?" was found. In this document the review question is "Identification by systematic review and meta-analysis of pre- and peri-operative individual patient factors that contribute to recurrence of giant ventral hernia following apparently curative surgery", the inclusion criteria "Studies reporting data from adult patients with giant ventral hernia who are undergoing surgery with curative intent", the types of study to be included "We intend to include all study designs, i.e. RCT, prospective case-control series, retrospective cohort studies", the primary outcome is: "Clinical recurrence of giant ventral hernia following surgery with curative intent. Recurrence will be defined as within 1-year following the index surgery" .

However, paper reviewed was entitled "A Systematic Methodological Review of Reported Perioperative Variables, Postoperative Outcomes and Hernia Recurrence from Randomised Controlled Trials of Elective Ventral Hernia Repair: Clear Definitions and Standardised Datasets are needed". The review question is "Our aim is to identify and quantify the inconsistencies in perioperative variable and postoperative outcome reporting, so as to justify future development of clear definitions of hernia recurrence and a standardised dataset of such variables", also "The target condition was surgical VH repair. All different VH morphologies were eligible...". The inclusion criteria "Adult participants having a surgical VH repair". The primary outcome "Our outcomes of primary interest were; hernia recurrence, the post-operative recurrence rates, the timing of recurrence, the definitions for VH recurrence used, and the test method(s) used to diagnose recurrence (for example clinical examination, CT scan, US scan)..."

It's quite difficult to 'connect' from a methodological point of view the reviewed paper and the PROSPERO registry CRD42016043071.

RESPONSE#2: The reviewer is correct. It is difficult initially to reconcile our submission with the PROSPERO entry, which is why we omitted the PROSPERO registration in our first submission. The PROSPERO registration refers to a protocol that has been developed by us in order to identify VH recurrence predictors via systematic review and subsequent meta-analysis (the protocol is currently being prepared for submission to a prognostic research journal). In our protocol, we hypothesize that comparative studies (RCTs, Cohort studies and Case-control studies) in VH are likely to present highly heterogeneous data reporting many different peri-operative variables and post-operative outcomes, thus making trial comparison difficult and impairing predictor identification. Indeed, in our protocol we explain that we plan to publish individual systematic reviews for each of the study designs encountered so that we can emphasise deficiencies in study level reporting. The current submission arises from the RCT review. In our PROSPERO entry, we state: 'We intend to include all study designs, i.e. RCT, prospective case-control series, retrospective cohort studies. If we encounter sufficient studies, we will report these as individual systematic reviews'. In addition we state: that 'data collected will be categorised into five broad categories as follows: study design; hernia morphology; preoperative patient factors including comorbidities; intraoperative variables; clinical outcome, including complication rates and hernia recurrence' much of this data from RCTs is included in this review. In essence, the current submission arises from a greater body of work dealing with VH recurrence prediction, and the PROSPERO registration encompasses the present review under this larger body of work.

This body of work is funded by the UK NIHR (National Institute for Health Research) RfPB (Research for Patient Benefit) scheme (PB-PG-0816-20005).

3)

- Authors answer: "It is not uncommon practice to limit systematic reviews to English Language, especially where facilities for translation are not in place (as was the case for us). A case for translation could be made well if the volume of research retrieved in English was limited, but we were able to find in excess of 30 RCTs, which is likely to

approach data saturation."

Reviewer comment: again, reading PRISMA statement in point 6 (The PRISMA checklist), item 6 (Eligibility Criteria) "Inclusion or not of non-English language literature...can influence the effect estimates in meta-analyses"

Restriction to only English language can be another methodological flaw.

RESPONSE#3: (As said previously) It is not uncommon practice to limit systematic reviews to English Language, especially where the facilities for translation are not in place. We have included a large number of studies which will represent the majority of the indexed literature on this topic. The data presented from these trials is heterogeneous; standardised datasets and clear definitions are warranted.

4)

- Authors answer: "PICO relates to evidence-based-medicine practice, which is somewhat different to systematic review. We have attempted to rephrase our title in PICO format but this has become unwieldy. We believe the current title represents the work well. If the Editor wishes us to change our title, we would be happy to adopt his suggestions."

Reviewer comment: reading out PRISMA statement again, in point 6 (The PRISMA checklist) item 4 (Objectives) "Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS)". Moreover, PRISMA follows "The questions being addressed, and the rationale for them, are one of the most critical parts of a systematic review. They should be stated precisely and explicitly so that readers can understand quickly the review's scope and the potential applicability of the review to their interests"

Failure to provide questions being addressed in a complete PICO format is a very important methodological flaw.

RESPONSE#4: A PICOS statement with this review is challenging as this is a methodological review and not analysing a single intervention with a single comparator. However, we have written a PICOS statement and included it in the introduction.

The PICOS sub-headings are below:

Population (P): Adults over the age of 18 under-going elective ventral hernia repair.

Intervention (I): Multiple different interventions all trying to improve the outcomes of elective ventral hernia repair e.g. laparoscopic VH repair, light weight mesh, double crown of tacks mesh fixation

Comparator (C): Multiple different comparators – e.g. open VH repair, heavy weight mesh, suture mesh fixation (respectively to above interventions).

Outcomes (O): The inconsistency of peri-operative variable and post-operative outcome reporting, paying particular attention to the different methods used to report and define ventral hernia recurrence.

Study design (S): Randomised Controlled Trials.

Our attempts at PICOS:

1)

The objective of this systematic review was to analyse the peri-operative variables and post-operative outcomes (O) reported by randomised controlled trials (S) (RCTs) of adult patients undergoing elective ventral hernia repair (P). We focused particularly on the variety of methods used to detect and define hernia recurrence. All ventral hernia repair RCTs were included irrespective of the intervention (I) and comparator (C) groups.

Our aim was to demonstrate the inconsistencies in variable and outcome reporting by RCTs and the necessity for standardised trial datasets as well as clear definitions of hernia recurrence and recurrence detection methods.

2)

In this systematic review, we analysed randomised controlled trials (S) of adult patients undergoing elective ventral hernia repair (P). All ventral hernia repair RCTs were included irrespective of the intervention (I) and comparator (C) groups. We analysed all perioperative variables and post-operative outcomes reported (O), paying particular attention to the different methods used to detect and define hernia recurrence.

Our objective was to demonstrate the inconsistencies in variable and outcome reporting by RCTs and the necessity for standardised trial datasets as well as clear definitions of hernia recurrence and recurrence detection methods.

We have included statement 2 in the revised submission.

## Title Page

### **A Systematic Methodological Review of Reported Perioperative Variables, Postoperative Outcomes and Hernia Recurrence from Randomised Controlled Trials of Elective Ventral Hernia Repair: Clear Definitions and Standardised Datasets are needed.**

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Conflict of Interest: Windsor A.C.J. declares conflicts of interest not directly related to the submitted work; educational grants and speaker for: BARD, LifeCell and Cook.

Parker S.G, Wood C, Butterworth J.W, Boulton R, Plumb A.A, Mallet S and Halligan S declare no conflict of interest.

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## A Systematic Methodological Review of Reported Perioperative Variables, Postoperative Outcomes and Hernia Recurrence from Randomised Controlled Trials of Elective VH Repair: Clear Definitions and Standardised Datasets are needed.

### Abstract

*Background* This systematic review assesses the perioperative variables and post-operative outcomes reported by randomised controlled trials (RCTs) of VH repair. This review focuses particularly on definitions of hernia recurrence and techniques used for detection.

*Objective* Our aim is to identify and quantify the inconsistencies in perioperative variable and postoperative outcome reporting, so as to justify future development of clear definitions of hernia recurrence and a standardised dataset of such variables.

*Methods* The PubMed database was searched for elective VH repair RCTs reported January 1995 to March 2016 inclusive. Three independent reviewers performed article screening, and two reviewers independently extracted data. Hernia recurrence, recurrence rate, timing and definitions of recurrence, and techniques used to detect recurrence were extracted. We also assessed reported post-operative complications, standardised operative outcomes, patient reported outcomes, pre-operative CT scan hernia dimensions, intra-operative variables, patient co-morbidity, and hernia morphology.

*Results* 31 RCTs (3367 patients) were identified. Only 6 (19.3%) defined hernia recurrence and methods to detect recurrence were inconsistent. Sixty-four different clinical outcomes were reported across the RCTs, with wound infection (30 trials, 96.7%), hernia recurrence (30, 96.7%), seroma (29, 93.5%), length of hospital stay (22, 71%) and haematoma (21, 67.7%) reported most frequently. Fourteen (45%), 11 (35%) and 0 trials reported CT measurements of hernia defect area, width and loss of domain respectively. No trial graded hernias using generally accepted scales.

*Conclusion* VH RCTs report peri- and post-operative variables inconsistently, and with poor definitions. A standardised minimum dataset, including definitions of recurrence, is required.



## Background

In an ageing population[1] with an increasing prevalence of both obesity[2] and abdominal surgery, the incidence of ventral hernia (VH) is increasing[3,4]. The projected number of VH repairs performed in 2016 in the United States approaches 400,000[3]. Recurrence rates after repair are high, reaching 10 to 40%[5],[6]. Incidence of large complex VH is also increasing and significant loss of domain coupled with comorbidity means these patients present the sternest surgical challenge[7]. Despite innovation[8–10] there is no consensus regarding optimal reconstructive techniques[11,12].

Currently, the VH literature consists primarily of case series and large observational studies. This level 4 evidence[13] suggests the cause of postoperative complications and hernia recurrence are complex and multifactorial. To date, research has focussed largely on surgical technique[12],[14] and patient co-morbidity[15,16] with limited focus on hernia morphology. Although several hernia grading scales have been produced[17–21], in an attempt to predict post-operative outcomes, few have been externally validated and, if so, with limited success[22–24]. Comparative trials and observational studies seldom define hernia recurrence and if they do, many use different definitions for recurrence as well as a variety of techniques to detect recurrence. Standardised definitions and validated datasets for VH repair studies would make reported data consistent, allowing for greater accuracy of trial comparison and meta-analysis.

In this systematic review, we analysed randomised controlled trials (RCTs) of adult patients undergoing elective VH repair. All VH repair RCTs were included irrespective of the intervention and comparator groups. We analysed all perioperative variables and post-operative outcomes reported, paying particular attention to the different methods used to detect and define hernia recurrence. Our objective was to demonstrate the inconsistencies in variable and outcome reporting by RCTs and the necessity for standardised trial datasets as well as clear definitions of hernia recurrence and recurrence detection methods.

## Methods

### *Reporting and Registration*

This systematic review was reported in line with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement[25]. Ethical permission is not required by our centre for systematic reviews of available primary literature. A protocol was developed and registered with PROSPERO, the international prospective register of systematic reviews (CRD42016043071).

### *Inclusion and exclusion criteria*

#### *Inclusion criteria for studies*

1 We aimed to identify RCTs that described clinical outcomes in patients following  
2 VH repair between 1<sup>st</sup> January 1995 and 31<sup>st</sup> March 2016 inclusive. We excluded  
3 trials with less than 10 patients in an individual study arm since such data are  
4 likely to be weak. Only RCTs written in English were included.  
5

### 6 *Target condition*

7  
8 The target condition was surgical VH repair. All different VH morphologies were  
9 eligible as were all VH working group (VHWG) grades[17]. Studies describing  
10 femoral and/or inguinal hernias (i.e. groin hernia) were excluded. Emergency VH  
11 repair was excluded as was primary closure after damage control laparotomy.  
12 However, patients having elective VH repair after primary closure from damage  
13 control laparotomy were eligible as were RCTs of elective VH repair with  
14 bridging repair (i.e. failure to establish primary fascial closure). RCTs of  
15 parastomal hernia repairs were excluded. Trials with concomitant bowel  
16 resection were included (since this is often intended) and as long as the primary  
17 objective of surgical repair was VH repair. We excluded trials with either  
18 concomitant tumour removal or bariatric surgery.  
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### 23 *Participants*

24  
25 Adult participants having a surgical VH repair. We excluded paediatric studies  
26 (defined as 18 years or less) since these are not representative of 'typical' CVH  
27 patients.  
28  
29

### 30 *Follow up*

31  
32 We stipulated no minimum length of follow-up.  
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### 36 *Comparison*

37  
38 There was no restriction placed on any study arm comparator (e.g. operative  
39 technique, mesh type, position of mesh).  
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### 42 *Search strategy and string*

43  
44 A surgical research fellow, SGP, searched the PubMed database from 1<sup>st</sup> January  
45 1995 to 31<sup>st</sup> March 2016 inclusive limiting the search using the following terms:  
46 "adult 19+", "human studies" and to those written in English. Our search string  
47 identified and combined the two following criteria to identify relevant articles:  
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- 50  
51 • To identify studies of VH disease including complex disease we used the  
52 MESH terms "hernia", "abdominal hernia", "umbilical hernia" and "VH" were  
53 used. These were combined with keywords: "abdominal wall reconstruction";  
54 "herniorrhaphy"; "ventral defect" and "entero-cutaneous fistula".
- 55  
56 • To identify studies of surgical techniques used for VH repair we used the  
57 MESH terms: "general surgery"; "reconstructive surgical procedures" and  
58 "surgical mesh". This was combined with keywords: "pneumoperitoneum",  
59 "botox", "botulinium", "two-stage", "two step", "staged repair", "component  
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1 separation", "transversus abdominis", "retro-rectus", "bridging", "bridge  
2 repair", "silo", "open" and "laparoscopic".

3  
4 Our complete search string is shown in online resource 1.

5  
6 *Citation management and screening*

7  
8 SGP stored identified citations in an Excel spreadsheet (Microsoft Excel for Mac  
9 2011 Version 14.5.9, Microsoft Corporation, Washington, USA), up-loading these  
10 subsequently into a reference manager able to access online original articles  
11 directly (Mendeley Desktop Version 1.17 for Windows XP and Mac OS X, London,  
12 UK). After the search filters were applied and duplicates were excluded, the  
13 citations were divided into two equal groups. The titles of the first-half of the  
14 citations were screened by SGP and the second-half by CW. The researchers  
15 screened for comparative studies of VH disease. They discarded articles that  
16 were 'clearly unsuitable' for the review (e.g. subject not VH) and retained any  
17 regarded as 'uncertain' or 'definitely possible'. These two latter groups were  
18 combined and researchers, SGP, CW and RB, then independently screened the  
19 titles and abstracts of the 'uncertain' and 'definitely possible' results with the aim  
20 of identifying all comparative studies. Any discrepancies were settled by face-to-  
21 face discussion amongst the three researchers. A third hand search of the full  
22 text by SGP, CW and RB, then divided the selected comparative studies into  
23 respective methodological designs; case-control studies, cohort studies and  
24 RCTs. Any article where uncertainty persisted was discussed with senior  
25 members, AW and SH, face-to-face. An exclusion log was kept at all stages. The  
26 PRISMA diagram (fig 1.) shows the flow of article selection.

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33 *Data extraction*

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35 SGP and JB extracted data independently from all RCTs selected for the review,  
36 which were cross-checked subsequently face-to-face. Data were entered by the  
37 researchers into an Excel datasheet and categorised into broad groups as  
38 follows: study design; hernia morphology; pre-operative patient factors  
39 including comorbidities; intraoperative variables and clinical outcomes,  
40 including complication rates and hernia recurrence.

41  
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45 *Study demographics and risk of bias*

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47 Information extracted for RCT study design included: the study setting (multi-  
48 centre vs. single centre), the country of publication, the date of publication and  
49 the number of patients in each study arm. Researchers, SGP and JB, used the  
50 Cochrane Collaboration's tool to assess the risk of bias[26]. Any differences in  
51 opinion were discussed face-to-face and settled by discussion with senior  
52 authors if required.

53  
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55  
56 *Hernia morphology*

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58 For hernia morphology, we intended to record dimensions of the hernia defect,  
59 including area, loss of domain, the ventral hernia working group (VHWG)

1 grade<sup>[17]</sup> and the CDC wound classification<sup>[27]</sup>. We recorded whether the study  
2 included patients with either primary or incisional VHs, or both, and if so the  
3 proportion of these two hernia types. However, we anticipated that many trials  
4 would not report these details of hernia morphology and grade, and recorded  
5 when these items were not reported. Similarly, we recorded the number of  
6 previous attempts at hernia repair where documented. We noted prior surgical  
7 site infection in patients undergoing repair since this is known to predispose to  
8 subsequent recurrence<sup>[15]</sup>.  
9

### 10 *Pre-operative patient characteristics and co-morbidities*

11  
12  
13 Baseline patient characteristics extracted were mean patient age and the  
14 proportion of male to females. Comorbidity data included the mean and standard  
15 deviation of body mass index (BMI), the proportion of patients with chronic  
16 obstructive pulmonary disease (COPD), diabetes, steroid use, and the proportion  
17 of each American Society of Anaesthesiologists (ASA) grade (and mean ASA  
18 grade) in each study group. Proportion by smoking status, arteriopath status  
19 (previous diagnosis of ischaemic heart disease (IHD), peripheral vascular disease  
20 (PVD), cerebrovascular accidents (CVAs)) and a diagnosis of benign prostatic  
21 hypertrophy (BPH) were also noted.  
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### 25 *Intra-operative variables*

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28 We recorded the mode of surgery used (e.g. laparoscopic or open), the type of  
29 mesh where used, the anatomical layer within the abdominal wall into which the  
30 mesh was implanted (i.e. intraperitoneal, pre-peritoneal, retro-rectus, inlay or  
31 onlay), operative duration, intra-operative blood loss, and the experience of the  
32 principal surgeon where documented.  
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### 36 *Reported Clinical Outcomes*

#### 37 *Hernia recurrence*

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41 Our outcomes of primary interest were; hernia recurrence, the post-operative  
42 recurrence rates, the timing of recurrence, the definitions for VH recurrence  
43 used, and the test method(s) used to diagnose recurrence (for example clinical  
44 examination, CT scan, US scan) were recorded. These data were analysed to  
45 investigate whether the method used to detect recurrence influenced recurrence  
46 rate. As we were aware of no generally accepted imaging definition of VH  
47 recurrence, we anticipated considerable inter-observer variability for reporting  
48 recurrence.  
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51  
52 We did not pre-specify the definition of post-operative hernia recurrence. We did  
53 not restrict by timing of recurrence, the definitions for VH recurrence used, or  
54 the test method(s) used to diagnose recurrence.  
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#### 57 *Secondary outcomes*

#### 58 *Post-operative complications*

1 All post-operative complications described were recorded. Complications were  
2 grouped into intraoperative, early postoperative, late post-operative, and  
3 general or standardised outcomes. Early postoperative complications were sub-  
4 grouped into local wound complications (wound infection, seroma formation,  
5 wound dehiscence, skin necrosis) and systemic complications (hospital acquired  
6 pneumonia, myocardial infarction, pulmonary embolism). Early post-operative  
7 complications were defined as those occurring within 30 days of surgery and late  
8 post-operative complications as those occurring thereafter. Late complications  
9 were extracted for the timespan presented in the paper.  
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### 13 *Standardised outcomes*

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16 Where reported, we recorded all standardised post-operative outcome measures  
17 used. We anticipated that RCTs would use a variety of outcome measures such as  
18 length of hospital stay, 30-day re-operation rate and 30-day re-admission rate. If  
19 trial complications were measured using a standardised post-operative  
20 complication scale, the value was recorded.  
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### 23 *Patient reported outcome measures*

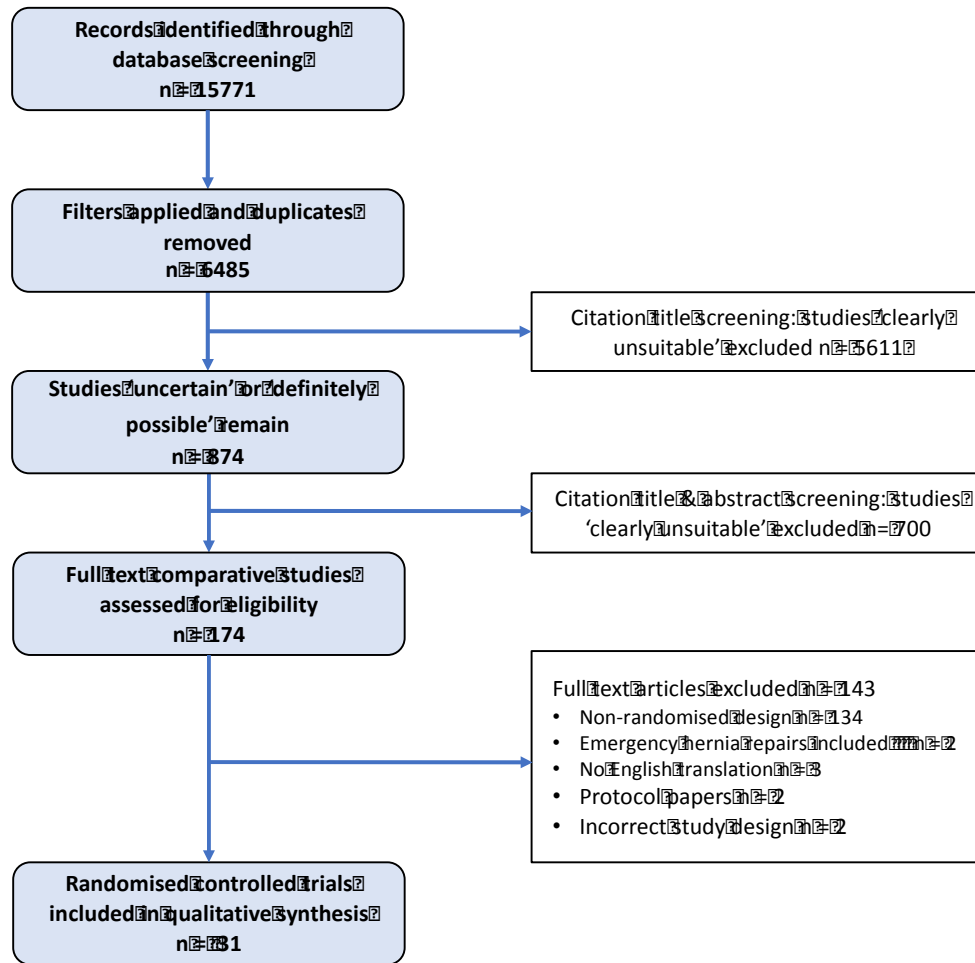
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26 We foresaw that some trials may use standardised patient reported outcome  
27 measures (PROMs) to measure operative success. These may include visual  
28 analogue scales for pain or overall health status. They may also report the time  
29 to first bowel movement or the time taken to return to normal activities. All such  
30 outcomes were recorded, along with the timing of the assessment.  
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## 33 **Results**

### 34 *Search results*

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38 Our initial search retrieved 15771 results (fig 1.). After applying search filters  
39 [studies published between 1<sup>st</sup> January 1995 to 31<sup>st</sup> March 2016, human trials  
40 only, participants aged  $\geq 19$ , studies written in English], we excluded 9286  
41 studies, resulting in 6485 papers for our initial review. After screening the  
42 citation titles, we ultimately categorised 874 studies as 'definitely possible' or  
43 'uncertain'. This fell to 174 comparative studies after title and abstract screening.  
44 The full text of all 174 articles was assessed for details of study methodology.  
45 This identified 31 RCTs included in the present systematic review.  
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Figure 1. PRISMA diagram showing selection of RCTs for this review



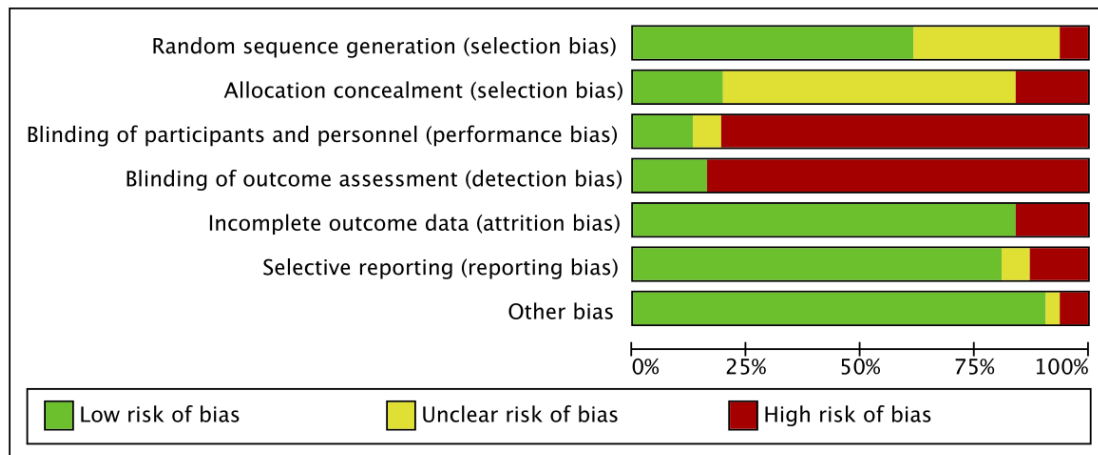
### Study demographics

Study demographics and design characteristics are shown in Table 1. The 31 RCTs included 3,367 patients with a mean of 109 patients, range 24 to 337. One study[28] appears twice since it divided patients into simple and complex hernia groups, creating two individual trials (suture vs mesh repair and prosthetic mesh vs auto-dermal graft repair). Five RCTs were carried out in both the Netherlands[29–33] and Spain[34–38]. Thirteen RCTs were multi-centre and 18 were single centre. Over the past 20 years the number of RCTs performed increased, with 8 published between 1995 to 2005 versus 23 published from 2005 to 2016. There were 3 groups where RCTs compared the same interventions: Eleven studies compared laparoscopic versus open repair; 5 studies[28,30,36,39,40] compared suture versus mesh repair and 3 studies[37,41,42] compared tack versus suture mesh fixation in laparoscopic VH repair.

Table 1. Demographic and characteristics of the 31 RCTs included in the Systematic Review.

<b>Included Studies - Demographics</b>		
<b>Characteristic</b>	<b>Subgroup</b>	<b>No. of RCTs</b>
<b>-Country of Publication</b>	Netherlands[29-33] Spain[34-38]	5
	India[41-43] Egypt[44-46]	3
	Pakistan[40],[47] Turkey[39],[48] Italy[49,50]Germany [28],[51]	2
	Sweden[52] USA[53] Australia[54] Lithuania[55] France[56] Belgium[57] Denmark[58]	1
<b>-Multi vs Single-centre</b>	Multi centre[28-30],[32-34],[40],[49],[51-53],[57-58]	13
	Single centre[31],[35-39],[41-46],[48-50],[54-56]	18
<b>-Year of Publication</b>	1995-2005[28],[30],[32],[35-36],[39],[46]	7
	2006-2016[29],[31],[33-34],[37-38],[40-45],[47-58]	24
<b>Included Studies</b>		
<b>Characteristic</b>	<b>Subgroup</b>	<b>No. of RCTs</b>
<b>-Trial Groups</b>	Laparoscopic vs. Open[29],[34-35],[43],[47-50],[52-54]	11
	Open mesh vs. suture[28],[30],[36],[39-40]	5
	Laparoscopic mesh fixation; Tacks vs. Sutures[31],[37],[41-42]	3
	• Open VH repair:	
	<i>Onlay vs. Sublay</i> [44],[55]	2
	<i>Light weight vs. Heavy weight mesh</i> [32]	1
	<i>Medium weight vs. Medium weight mesh</i> [51]	1
	<i>Autograft vs. Prosthetic mesh</i> *[28*]	1
	<i>Component separation vs. Prosthetic mesh</i> [33]	1
	<i>Onlay vs. Underlay</i> [45]	1
	<i>Intraperitoneal vs. Onlay /bridging</i> [46]	1
	<i>Ventrex patch vs Biomesh composite mesh</i> [56]	1
	• Laparoscopic VH repair:	
	<i>Double crown tack vs. suture and tack mesh fixation</i> [31],[57]	2
	<i>Double crown tack vs. fibrin sealant mesh fixation</i> [58]	1
	<i>Light weight mesh vs. Medium weight mesh</i> [38]	1
	Total	32*
	*Large hernias from Korenkov et al. (a suture vs. mesh RCT) were analysed as a separate category. This makes this total 32 rather than 31.	
<b>-Hernia type</b>	Primary hernias only[36],[39-40],[44-45],[47]	6
	Incisional hernias only[28-30],[32-34],[38],[46],[49-53],[55]	14
	Primary and incisional hernias[31],[35],[37],[41-43],[48],[54],[56-58]	11
<b>-Primary outcomes</b>	Hernia recurrence[28],[49],[54],[56]	4
	Quality of life/ Health questionnaires[32],[34],[51-52]	4
	Pain [measured using visual analogue scores][29],[31],[57],[58]	4
	Pain and hernia recurrence [two primary outcomes][38]	1
	Mesh shrinkage[37]	1
	Total complications rates[53]	1
	Unclear[30],[33],[35-36],[39-48],[50],[55]	16
<b>-Risk of Bias: Cochrane Collaboration's tool</b>	High risk of bias[28-50],[52-58]	30
	Low risk of bias[51]	1

Figure 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.



### *Risk of bias and study design*

Thirty RCTs were assessed as at high risk of bias with just one[51] considered at low risk. Figure 2 shows that this high level of bias is mostly due to the failed blinding of trial participants, personnel (surgeons) and outpatient assessors. Only two trials[32],[51] achieved blinding for both these criteria.

### *Hernia morphology*

Twenty-three of 30 (76.6%) RCTs used hernia dimensions as an inclusion criteria and one RCT[28] divided hernias into simple and complex categories using a 10cm defect width cutpoint. Seven trials had no selection criteria that used hernia dimension. The exact nature of dimension inclusion criteria varied across trials, ranging from hernias with a width of less than 4cm[39], to hernias with a width of greater than 10cm[28,46]. Fourteen trials (45.2%) recorded the average defect surface area, which ranged from 3.4cm<sup>2</sup> to 141.2cm<sup>2</sup>, with a mean of 43.1cm<sup>2</sup>. Eleven trials (35.5%) recorded the average or median hernia width within each comparison group, which ranged from 3.6cm to 17cm with a mean of 7.5cm. None of the RCTs reported loss of domain or used loss of domain for patient selection (Table 2.).

As anticipated, no RCT recorded either VHWG grade or CDC wound classification of included hernias. Indeed, no RCT used a VH grading scale of any description. Six trials (19.3%) included primary VHS only, 14 trials (45.2%) included incisional hernias only, and 11 trials (35.5%) included both primary and incisional hernias. Ten of these 11 trials, including both primary and incisional VHS, reported the proportion of primary to incisional hernias, with a mean of 32 primary to 41 incisional hernias (range 31:7[58] to 18:65[57]). Seven of the 25 trials (28%) analysing incisional hernias included the ratio of primary incisional hernias to recurrent incisional hernias (mean of 84.1 primary to 28.3 incisional hernias, range 160:3[49] to 24:30[28]). Only two trials [30,47] reported the number of patients with previous ventral wound infection.



Table 2. Summarising the hernia morphology data reported.

<i>Hernia dimension</i>	<i>No. of RCTs reporting variable</i>
Average hernia defect surface area	14[30-31],[35],[37-38],[41],[43],[50],[52-57]
Average hernia defect width	11[28,29],[32-34],[38],[40],[44],[49-50],[52]
Loss of Domain	0

*Pre-operative patient characteristics and co-morbidities*

Table 3 summarises the patient characteristics and comorbidities reported. The pre-operative patient characteristics and comorbidities reported differed between trials. While many reported basic patient demographics of age, gender and BMI, few went beyond this to report patient comorbidities, including smoking status, diabetic status and steroid use.

Table 3. Preoperative patient characteristics and comorbidities reported.

<i>Patient characteristic/comorbidities</i>	<i>No. of RCTs reporting variable</i>
Age [mean]	30[28-39],[41-58]
Gender [male/female ratio]	29[28-39],[41-50],[52-58]
Obesity [as a ratio >/< 35 or mean [SD]]	23[28-34],[37-38],[41-45],[48-50],[51-53],[55-58]
No. patients ASA 3	10[29],[31],[36-37],[39],[45],[49],[51-53]
COPD	8[28],[34],[38],[43],[45],[51-53]
Smoking status	8[28],[30],[45],[51-53],[56-57]
No. patients with Diabetes	7[34],[38],[44],[51-53],[56]
No. patients ASA 1	7[29],[31],[45],[49],[51-53]
No. patients ASA 2	7[29],[31],[45],[49],[51-53]
SF-36 QoL questionnaire <sup>[59]</sup>	3[32],[51],[52]
No. patients using steroids	3[28],[51],[53]
No. of arteriopathies [IHD/PVD/CVA]	3[28],[44],[52]
No. patients ASA 4	3[29],[49],[51]
Average ASA score	2[34],[55]
Liver cirrhosis / Childs-Pugh A	1[44]
SF-12 QoL questionnaire <sup>[59]</sup>	1[56]

*Intra-operative variables*

Table 4 shows that intraoperative variables were reported with increased frequency compared to pre-operative variables and patient comorbidities. Mode of surgery, type of mesh implanted (prosthetic, composite, biosynthetic or biologic) and anatomical layer were recorded in all 31 RCTs. Operation duration, intra-operative blood loss and the experience of the principal operating surgeon were all reported less frequently.

Table 4. Intra-operative variables reported.

<b>Intra-operative variable</b>	<b>No. of RCTs reporting variable</b>
Mode of Surgery [laparoscopic/open]	31[28-58]
Category of mesh used	31[28-58]
Anatomical layer of mesh placement	31[28-58]
Duration of operation	27[28-31],[33-45],[48-50],[52-58]

Experience of the principal surgeon	14[29],[31],[33-34],[36],[46-47],[49],[52-55],[57-58]
Intra-operative blood loss	3[29],[33],[43]

### *Clinical outcomes*

Sixty-four different clinical outcomes were reported overall, with little consistency between trials, even when reporting similar intervention groups and primary outcomes. Indeed, 16 (51.6%) RCTs stated no primary outcome explicitly (Table 1). Of the 15 RCTs (48.4%) stating a primary outcome; 4[28,49,54,56] used hernia recurrence and 4[32,34,51,52] employed quality of life. Three trials[32],[51,52] used the SF-36 questionnaire[59] and 1 trial[34] used the EQ-5D questionnaire[60]. Four trials[29,31,57,58] used pain as their primary outcome, assessed via visual analogue scales (VASs). One trial stated both pain and recurrence as two separate primary outcomes, with no statistical accounting for co-primary outcomes[38]. The remaining two trials used mesh shrinkage[37] or standardised complication rates[53] as their primary outcomes respectively. Multiple different primary outcomes led to many different clinical and patient reported outcomes (as shown in online resource 2).

Length of follow-up was reported in all studies and averaged 24.5 months (range 1 month to 64 months). Fifteen of 31 (48%) trials had follow-up of at least 24 months. One trial[52] did not report hernia recurrence rate. Of the 30 trials reporting hernia recurrence, 1 RCT[36] reported recurrence at 5 years post repair, 4 RCTs[29-30],[41],[56] reported recurrence at 3 years, 15 RCTs at 2 years, 13 RCTs at 1 year, 5 RCTs[37],[41],[43],[50-51] at 6 months and 1 RCT[34] at 3 months. Six (20%) of 30 RCTs defined recurrence: definitions are shown in table 5. Only three trials used the same definition. Eight (29%) of 30 trials did not specify the method used to detect recurrence. Twelve trials (43%) used clinical examination alone to detect recurrence. Ten (33%) trials used imaging if recurrence was in doubt, or to confirm a recurrence suspected clinically. Five (50%) of these 10 trials[29,31,33,43,57] used either CT or USS to detect recurrence, 3 (30%) trials[30,42,58] used USS alone and 2 (20%) trials[38,46] used CT alone. Recurrence rates increased when imaging was used. Trials using clinical examination had a 4% median recurrence rate whereas trials using USS or CT, USS alone, or CT alone had median recurrence rates of 7%, 9% and 7% respectively. Trials that did not specify test methods for recurrence had a mean re-herniation rate of 7%. The method used to detect hernia recurrence did not depend on the size or type of hernia included in the trial (as shown in online resource 3). Patient reported outcomes used the SF-36[59], SF-12[59], EQ-5D[60], and GIQL[62] questionnaires as well as VASs, to assess pain and overall health status. These were also carried out at varying time intervals. The Calvien-Dindo[61] scale for post-operative complications was used in 9 of the trials to classify complication severity.

Table 5. Six definitions of hernia recurrence encountered in the systematic review.

Reference:	Definition
Arroyo et al.[36] (2001)	'the presence of a defect on the central part of the midline aponeurosis around the umbilicus, where the operation had been performed

1 2 3 4 5	Bensaadi et al.[56] (2014) Lal et al.[40] (2012)	previously.' 'a defect of the midline aponeurosis around the umbilicus at the site where the operation was performed.' 'the presence of a defect on the central part of the midline aponeurosis where the operation had been performed previously.'
6 7 8	Luijendijk et al.[30] (2000)	'any fascial defect that was palpable or detected by ultrasound examination and was located within 7cm of the site of hernia repair.'
9 10	Pring et al.[54] (2008)	'a clinically detectable defect, associated with the protrusion of viscera on straining'.
11 12 13 14	Muysoms et al.[57] (2013)	'Patients were considered free from recurrence if at clinical examination, no hernia was felt in an upright position during valsalva manoeuver.'

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## Discussion

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This systematic review has analysed the reported perioperative variables and postoperative outcomes from randomised controlled trials of elective VH repair, performed over the last twenty years. Important findings include the general absence of: a standardised pre-operative patient variable dataset; a universally accepted definition of recurrence; standardised test methods to detect recurrence; standardised assessment times for the key primary and secondary outcomes, and standardised evaluation tools for post-operative pain and quality of life. This lack of standardisation limits the validity of trial comparisons made by meta-analyses and comparison of trials by practicing surgeons. Our review provides evidence-based justification for urgent investment in a core perioperative and clinical outcome dataset applicable to trials of VH surgery. This should be developed and validated with key stakeholders to improve the quality of outcome reporting in this rapidly developing field. A group such as COMET needs identification and encouragement to help develop and endorse this work[63].

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As VH research evolves, academics are searching increasingly for outcome predictors. Potentially reliable predictors can be identified from the primary literature only when they are reported. Our review has found that randomised controlled trials are focusing on surgical technique and failing to report variables that would normally be regarded as important predictors. For example, many pre-operative patient comorbidities and, in particular, measures of hernia morphology (e.g. hernia width and area) were omitted from most reports. Loss of domain was not reported by any trial. Because current evidence is contradictory, with some studies suggesting that hernia width does correlate with recurrence[64] whereas others do not[65,66], future trials need to report apparently important predictors to facilitate subsequent analysis. Investigators should also grade hernias using appropriate scales, for example the VHWG scale[17] and the CDC wound classification scale[27] as these scales themselves may prove to be outcome predictors. Our review demonstrates that a trial dataset with multiple pre-operative patient variables (diabetes, COPD, BMI, hernia grade etc), including pre-operative CT scan dimensions (hernia defect area, hernia width, loss of domain etc) and intra-operative variables (operation

1 time, anatomical plane of mesh insertion, reconstructive technique etc) is  
2 required.

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4 While 8 of the 30 trials (26.7%) reporting hernia recurrence didn't even define  
5 how recurrence was detected, the remaining trials used differing recurrence  
6 detection methods ranging from undefined clinical examination to undefined  
7 imaging methods. This introduces bias depending on the differing examination  
8 and imaging methods used. There was much variation in the timing of  
9 assessment for hernia recurrence. This observed lack of consensus regarding  
10 assessment timing, test methods for recurrence, and definitions of recurrence  
11 limits data availability and consistency, and impairs meta-analysis. To achieve  
12 standardisation a clear definition of VH recurrence is required. Imaging is likely  
13 the most precise method with which to determine recurrence, but a radiological  
14 definition of recurrence is required that incorporates measures of clinically  
15 important and unimportant reherniation. Currently, there is considerable  
16 variability in recurrence reporting for CT scans[67]. Our review suggests that the  
17 use of imaging does increase reported recurrence rates, which would be  
18 anticipated since subclinical recurrences will be identified.  
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23 RCT dataset designers should also consult the recommendations made by  
24 Muysoms et al. following a consensus meeting in Palermo, Italy in 2012[68]. This  
25 work gives detailed advice on how to carry out statistically sound research  
26 (interventional studies, observational studies, systematic review, and meta-  
27 analysis) in abdominal wall repair. Of particular relevance, this article advises  
28 using the EuraHS definition for hernia recurrence[69]; *"a protrusion of the*  
29 *contents of the abdominal cavity or preperitoneal fat through a defect in the*  
30 *abdominal wall at the site of a previous repair of an abdominal wall hernia"*, which  
31 we support, although (as stated above) a future definition of recurrence that  
32 includes radiological detection maybe more accurate but requires development.  
33 Muysoms et al. recommend using the EHS hernias classifications scales and  
34 measuring post-operative complications using the Clavien-Dindo classification  
35 system but do not define or list any other peri-operative or post-operative  
36 outcome variables that sound be measured. Importantly, they do allow for  
37 variability in the method used for recurrence detection and the time to  
38 outpatient assessment, which we feel this should be standardised, especially in  
39 RCTs. To standardise trial outcomes, a dataset with clear definitions and follow  
40 up assessment times is warranted.  
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47 A standardised dataset should include tools to assess chronic pain and quality of  
48 life (QoL). When comparing different surgical techniques, chronic pain and QoL  
49 are important patient-centred endpoints, as patients frequently place more  
50 emphasis on these outcomes than the operative surgeon. In this review, simple  
51 visual analogue scales were used commonly to assess pain. However, these  
52 analogue scales, and the timings of assessment were not standardised. A future  
53 dataset must standardise pain assessment. QoL was measured using many  
54 different questionnaires (SF-36[59], SF-12[59], EuroQoL[60] and GIQL[62]).  
55 These questionnaires are commonly used and they allow for health economic  
56 analysis across different disease states. However, they are not disease specific,  
57 and may miss important patient reported outcomes specific to hernia surgery.  
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1 Due to the unique set of complications arising from VH surgery, the importance  
2 of chronic pain and QoL, a hernia-specific patient reported outcome assessment  
3 tool, such as the Carolinas Comfort Scale[70] or the EuraHS-QoL  
4 questionnaire[69], should be used.  
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6 When constructing a VH perioperative variable and postoperative outcome  
7 dataset for randomised control trials, workers should also consult the VH  
8 databases currently being used in America[71], Europe[69], Denmark[72] and  
9 Spain[73]. These databases collect data prospectively from large cohorts of  
10 patients and will generate sizeable observational studies. These databases have  
11 been constructed by VH experts with multiple peri-operative and post-operative  
12 data-points, many of which should be included in an RCT dataset.  
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16 As well as focusing on standardised definitions and datasets, academic surgeons  
17 carrying out RCTs should make concerted efforts to reduce trial bias. Thirty of  
18 the 31 included trials were assessed as at high risk of bias. Many of the included  
19 trials performed poorly in 3 out of the 7 domains of the Cochrane Collaboration's  
20 tool for risk of bias[26]. Many trials failed to specify how participant group  
21 allocation was concealed, failed to blind participant and surgeon from the  
22 allocated treatment, and there was no blinding in the outpatient assessment  
23 clinic. Traditionally, surgical trials are usually at high risk of bias due to the  
24 impossibility of blinding the primary surgeon. However, if visible skin changes to  
25 the participant do not differ between the treatment groups [e.g. open VH repair  
26 with onlay vs. sublay mesh], it is possible to blind both the participant and an  
27 independent assessor. In addition, concealment of treatment allocation should  
28 follow the standards set by the Cochrane Collaboration. In surgery, the allocated  
29 treatment should only be revealed to an independent surgeon after the  
30 participant is under general anaesthetic and after the participant has been  
31 consented to take part in the trial and both possible treatments.  
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37 Further bias can arise in RCTs due to commercial funding and readers should be  
38 aware of this. We accept there are difficulties in achieving non-commercial  
39 funding for RCTs in hernia research and that without proper funding scrupulous  
40 methodology can be challenging due to the high work load. Eight out of 31 one of  
41 the trials received commercial funding[31,32],[37],[51],[54],[56-58], one trial  
42 received non-commercial funding[53] and one trial received both commercial  
43 and non-commercial funding[52]. In the remaining 21 trials the funding method  
44 was not specified. The practical difficulty of obtaining non-commercial funding  
45 can only be addressed by researchers, who whilst applying for funding must  
46 clearly explain the technical difficulties faced by reconstructive surgeons and the  
47 high prevalence of morbidity suffered by patients after hernia repair; namely  
48 chronic pain and recurrence. If researchers face difficulties with funding or  
49 carryout research with commercial funding, little can be done apart from  
50 carrying out research to highest possible standards. We note that any data is  
51 better than no data, as supported by Lilford et al[74].  
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## 57 **Conclusion**

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1 So far systematic reviews of elective VH RCTs have focused on comparing the  
2 outcomes of open versus laparoscopic VH repair[75],[76],[77]. This review is the  
3 first to assesses the methodology of VH RCTs. The results show that the  
4 perioperative variables and postoperative outcomes reported by RCTs of VH  
5 repair lack definition and consistency. To solve this, a defined minimum dataset  
6 of variables and outcomes is required. Since operative success is determined by  
7 the presence or absence of hernia recurrence, recurrence is therefore the prime  
8 outcome and requires standard clinical and radiological definitions, together  
9 with a minimum period of follow-up. For a clinical definition, we recommend  
10 using the European definition for hernia recurrence[69], and that a radiological  
11 definition requires development. Such measures will standardise and therefore  
12 improve outcome reporting in this rapidly expanding and important field,  
13 increasing data homogeneity and the value of subsequent meta-analysis.  
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7 **A Systematic Methodological Review of Reported Perioperative Variables,**  
8 **Postoperative Outcomes and Hernia Recurrence from Randomised**  
9 **Controlled Trials of Elective VH Repair: Clear Definitions and Standardised**  
10 **Datasets are needed.**

11 **Abstract**

12 *Background* This systematic review assesses the perioperative variables and  
13 post-operative outcomes reported by randomised controlled trials (RCTs) of VH  
14 repair. This review focuses particularly on definitions of hernia recurrence and  
15 techniques used for detection.

16 *Objective* Our aim is to identify and quantify the inconsistencies in perioperative  
17 variable and postoperative outcome reporting, so as to justify future  
18 development of clear definitions of hernia recurrence and a standardised dataset  
19 of such variables.

20 *Methods* The PubMed database was searched for elective VH repair RCTs  
21 reported January 1995 to March 2016 inclusive. Three independent reviewers  
22 performed article screening, and two reviewers independently extracted data.  
23 Hernia recurrence, recurrence rate, timing and definitions of recurrence, and  
24 techniques used to detect recurrence were extracted. We also assessed reported  
25 post-operative complications, standardised operative outcomes, patient  
26 reported outcomes, pre-operative CT scan hernia dimensions, intra-operative  
27 variables, patient co-morbidity, and hernia morphology.

28 *Results* 31 RCTs (3367 patients) were identified. Only 6 (19.3%) defined hernia  
29 recurrence and methods to detect recurrence were inconsistent. Sixty-four  
30 different clinical outcomes were reported across the RCTs, with wound infection  
31 (30 trials, 96.7%), hernia recurrence (30, 96.7%), seroma (29, 93.5%), length of  
32 hospital stay (22, 71%) and haematoma (21, 67.7%) reported most frequently.  
33 Fourteen (45%), 11 (35%) and 0 trials reported CT measurements of hernia  
34 defect area, width and loss of domain respectively. No trial graded hernias using  
35 generally accepted scales.

36 *Conclusion* VH RCTs report peri- and post-operative variables inconsistently, and  
37 with poor definitions. A standardised minimum dataset, including definitions of  
38 recurrence, is required.

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7 **Background**

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9 In an ageing population[1] with an increasing prevalence of both obesity[2] and  
10 abdominal surgery, the incidence of ventral hernia (VH) is increasing[3,4]. The  
11 projected number of VH repairs performed in 2016 in the United States  
12 approaches 400,000[3]. Recurrence rates after repair are high, reaching 10 to  
13 40%[5],[6]. Incidence of large complex VH is also increasing and significant loss  
14 of domain coupled with comorbidity means these patients present the sternest  
15 surgical challenge[7]. Despite innovation[8–10] there is no consensus regarding  
16 optimal reconstructive techniques[11,12].

17  
18 Currently, the VH literature consists primarily of case series and large  
19 observational studies. This level 4 evidence[13] suggests the cause of  
20 postoperative complications and hernia recurrence are complex and  
21 multifactorial. To date, research has focussed largely on surgical  
22 technique[12],[14] and patient co-morbidity[15,16] with limited focus on hernia  
23 morphology. Although several hernia grading scales have been produced[17–  
24 21], in an attempt to predict post-operative outcomes, few have been externally  
25 validated and, if so, with limited success[22–24]. Comparative trials and  
26 observational studies seldom define hernia recurrence and if they do, many use  
27 different definitions for recurrence as well as a variety of techniques to detect  
28 recurrence. Standardised definitions and validated datasets for VH repair studies  
29 would make reported data consistent, allowing for greater accuracy of trial  
30 comparison and meta-analysis.

31 ~~In this systematic review, we analysed randomised controlled trials (RCTs) of~~  
32 ~~adult patients undergoing elective VH repair. All VH repair RCTs were included~~  
33 ~~irrespective of the intervention and comparator groups. We analysed all~~  
34 ~~perioperative variables and post-operative outcomes reported, paying particular~~  
35 ~~attention to the different methods used to detect and define hernia recurrence.~~  
36 ~~Our objective was to demonstrate the inconsistencies in variable and outcome~~  
37 ~~reporting by RCTs and the necessity for standardised trial datasets as well as~~  
38 ~~clear definitions of hernia recurrence and recurrence detection methods.~~  
39 ~~Currently, rigorous level 1 research is relatively lacking. We anticipated that~~  
40 ~~RCTs of VH repair use a variety of comparison groups, report different~~  
41 ~~preoperative and intraoperative variables, and study multiple clinical outcomes.~~  
42 ~~Consequently, we hypothesised that the published RCTs' report highly~~  
43 ~~heterogeneous data. Our objective was to investigate this hypothesis by~~  
44 ~~systematic review, paying particular attention to the definitions and methods~~  
45 ~~used to report hernia recurrence.~~

Commented [SP1]: PICOS added

46 **Methods**

47 *Reporting and Registration*

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50 This systematic review was reported in line with the Preferred Reporting Items  
51 for Systematic Reviews and Meta-Analyses (PRISMA) statement[25]. Ethical  
52 permission is not required by our centre for systematic reviews of available  
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7 primary literature. A protocol was developed and registered with PROSPERO,  
8 the international prospective register of systematic reviews (CRD42016043071).

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10 *Inclusion and exclusion criteria*

11 *Inclusion criteria for studies*

12  
13 We aimed to identify RCTs that described clinical outcomes in patients following  
14 VH repair between 1<sup>st</sup> January 1995 and 31<sup>st</sup> March 2016 inclusive. We excluded  
15 trials with less than 10 patients in an individual study arm since such data are  
16 likely to be weak. Only RCTs written in English were included.

17  
18 *Target condition*

19  
20 The target condition was surgical VH repair. All different VH morphologies were  
21 eligible as were all VH working group (VHWG) grades[17]. Studies describing  
22 femoral and/or inguinal hernias (i.e. groin hernia) were excluded. Emergency VH  
23 repair was excluded as was primary closure after damage control laparotomy.  
24 However, patients having elective VH repair after primary closure from damage  
25 control laparotomy were eligible as were RCTs of elective VH repair with  
26 bridging repair (i.e. failure to establish primary fascial closure). RCTs of  
27 parastomal hernia repairs were excluded. Trials with concomitant bowel  
28 resection were included (since this is often intended) and as long as the primary  
29 objective of surgical repair was VH repair. We excluded trials with either  
30 concomitant tumour removal or bariatric surgery.

31  
32 *Participants*

33  
34 Adult participants having a surgical VH repair. We excluded paediatric studies  
35 (defined as 18 years or less) since these are not representative of 'typical' CVH  
36 patients.

37  
38 *Follow up*

39  
40 We stipulated no minimum length of follow-up.

41  
42 *Comparison*

43  
44 There was no restriction placed on any study arm comparator (e.g. operative  
45 technique, mesh type, position of mesh).

46  
47 *Search strategy and string*

48  
49 A surgical research fellow, SGP, searched the PubMed database from 1<sup>st</sup> January  
50 1995 to 31<sup>st</sup> March 2016 inclusive limiting the search using the following terms:  
51 "adult 19+", "human studies" and to those written in English. Our search string  
52 identified and combined the two following criteria to identify relevant articles:  
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- To identify studies of VH disease including complex disease we used the MESH terms “hernia”, “abdominal hernia”, “umbilical hernia” and “VH” were used. These were combined with keywords: “abdominal wall reconstruction”; “herniorrhaphy”; “ventral defect” and “entero-cutaneous fistula”.
  - To identify studies of surgical techniques used for VH repair we used the MESH terms: “general surgery”; “reconstructive surgical procedures” and “surgical mesh”. This was combined with keywords: “pneumoperitoneum”, “botox”, “botulinium”, “two-stage”, “two step”, “staged repair”, “component separation”, “transversus abdominis”, “retro-rectus”, “bridging”, “bridge repair”, “silo”, “open” and “laparoscopic”.

17 Our complete search string is shown in online resource 1.

#### 18 19 *Citation management and screening*

20  
21 SGP stored identified citations in an Excel spreadsheet (Microsoft Excel for Mac  
22 2011 Version 14.5.9, Microsoft Corporation, Washington, USA), up-loading these  
23 subsequently into a reference manager able to access online original articles  
24 directly (Mendeley Desktop Version 1.17 for Windows XP and Mac OS X, London,  
25 UK). After the search filters were applied and duplicates were excluded, the  
26 citations were divided into two equal groups. The titles of the first-half of the  
27 citations were screened by SGP and the second-half by CW. The researchers  
28 screened for comparative studies of VH disease. They discarded articles that  
29 were ‘clearly unsuitable’ for the review (e.g. subject not VH) and retained any  
30 regarded as ‘uncertain’ or ‘definitely possible’. These two latter groups were  
31 combined and researchers, SGP, CW and RB, then independently screened the  
32 titles and abstracts of the ‘uncertain’ and ‘definitely possible’ results with the aim  
33 of identifying all comparative studies. Any discrepancies were settled by face-to-  
34 face discussion amongst the three researchers. A third hand search of the full  
35 text by SGP, CW and RB, then divided the selected comparative studies into  
36 respective methodological designs; case-control studies, cohort studies and  
37 RCTs. Any article where uncertainty persisted was discussed with senior  
38 members, AW and SH, face-to-face. An exclusion log was kept at all stages. The  
39 PRISMA diagram (fig 1.) shows the flow of article selection.

#### 40 41 *Data extraction*

42 SGP and JB extracted data independently from all RCTs selected for the review,  
43 which were cross-checked subsequently face-to-face. Data were entered by the  
44 researchers into an Excel datasheet and categorised into broad groups as  
45 follows: study design; hernia morphology; pre-operative patient factors  
46 including comorbidities; intraoperative variables and clinical outcomes,  
47 including complication rates and hernia recurrence.

#### 48 49 *Study demographics and risk of bias*

50  
51 Information extracted for RCT study design included: the study setting (multi-  
52 centre vs. single centre), the country of publication, the date of publication and  
53 the number of patients in each study arm. Researchers, SGP and JB, used the

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7 Cochrane Collaboration's tool to assess the risk of bias[26]. Any differences in  
8 opinion were discussed face-to-face and settled by discussion with senior  
9 authors if required.

#### 10 *Hernia morphology*

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12 For hernia morphology, we intended to record dimensions of the hernia defect,  
13 including area, loss of domain, the ventral hernia working group (VHWG)  
14 grade<sup>[17]</sup> and the CDC wound classification[27]. We recorded whether the study  
15 included patients with either primary or incisional VHs, or both, and if so the  
16 proportion of these two hernia types. However, we anticipated that many trials  
17 would not report these details of hernia morphology and grade, and recorded  
18 when these items were not reported. Similarly, we recorded the number of  
19 previous attempts at hernia repair where documented. We noted prior surgical  
20 site infection in patients undergoing repair since this is known to predispose to  
21 subsequent recurrence[15].  
22

#### 23 *Pre-operative patient characteristics and co-morbidities*

24  
25 Baseline patient characteristics extracted were mean patient age and the  
26 proportion of male to females. Comorbidity data included the mean and standard  
27 deviation of body mass index (BMI), the proportion of patients with chronic  
28 obstructive pulmonary disease (COPD), diabetes, steroid use, and the proportion  
29 of each American Society of Anaesthesiologists (ASA) grade (and mean ASA  
30 grade) in each study group. Proportion by smoking status, arteriopath status  
31 (previous diagnosis of ischaemic heart disease (IHD), peripheral vascular disease  
32 (PVD), cerebrovascular accidents (CVAs)) and a diagnosis of benign prostatic  
33 hypertrophy (BPH) were also noted.

#### 34 *Intra-operative variables*

35  
36 We recorded the mode of surgery used (e.g. laparoscopic or open), the type of  
37 mesh where used, the anatomical layer within the abdominal wall into which the  
38 mesh was implanted (i.e. intraperitoneal, pre-peritoneal, retro-rectus, inlay or  
39 onlay), operative duration, intra-operative blood loss, and the experience of the  
40 principal surgeon where documented.  
41

#### 42 *Reported Clinical Outcomes*

##### 43 *Hernia recurrence*

44  
45 Our outcomes of primary interest were; hernia recurrence, the post-operative  
46 recurrence rates, the timing of recurrence, the definitions for VH recurrence  
47 used, and the test method(s) used to diagnose recurrence (for example clinical  
48 examination, CT scan, US scan) were recorded. These data were analysed to  
49 investigate whether the method used to detect recurrence influenced recurrence  
50 rate. As we were aware of no generally accepted imaging definition of VH  
51 recurrence, we anticipated considerable inter-observer variability for reporting  
52 recurrence.  
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8 We did not pre-specify the definition of post-operative hernia recurrence. We did  
9 not restrict by timing of recurrence, the definitions for VH recurrence used, or  
10 the test method(s) used to diagnose recurrence.

#### 11 *Secondary outcomes*

##### 12 *Post-operative complications*

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14  
15 All post-operative complications described were recorded. Complications were  
16 grouped into intraoperative, early postoperative, late post-operative, and  
17 general or standardised outcomes. Early postoperative complications were sub-  
18 grouped into local wound complications (wound infection, seroma formation,  
19 wound dehiscence, skin necrosis) and systemic complications (hospital acquired  
20 pneumonia, myocardial infarction, pulmonary embolism). Early post-operative  
21 complications were defined as those occurring within 30 days of surgery and late  
22 post-operative complications as those occurring thereafter. Late complications  
23 were extracted for the timespan presented in the paper.

##### 24 *Standardised outcomes*

25  
26  
27 Where reported, we recorded all standardised post-operative outcome measures  
28 used. We anticipated that RCTs would use a variety of outcome measures such as  
29 length of hospital stay, 30-day re-operation rate and 30-day re-admission rate. If  
30 trial complications were measured using a standardised post-operative  
31 complication scale, the value was recorded.

##### 32 *Patient reported outcome measures*

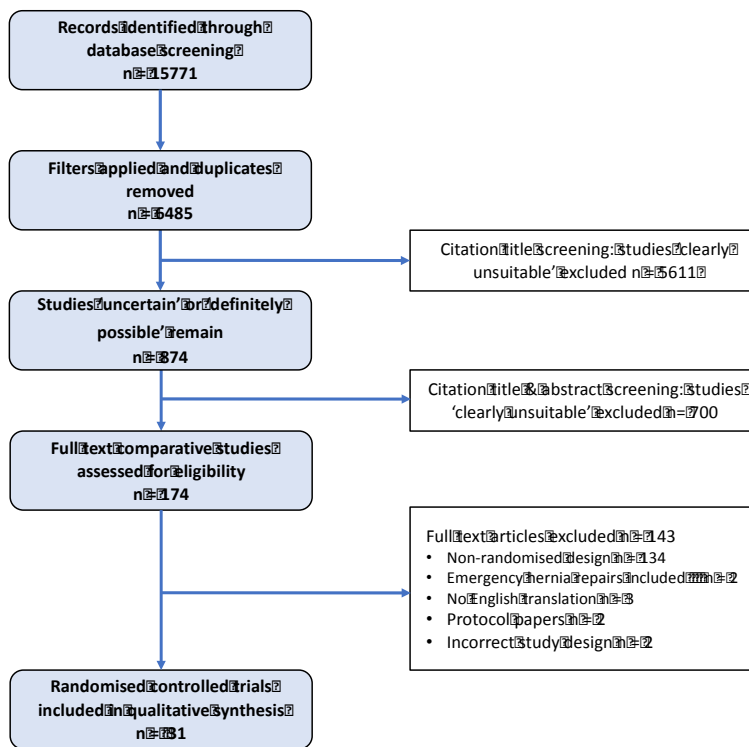
33  
34 We foresaw that some trials may use standardised patient reported outcome  
35 measures (PROMs) to measure operative success. These may include visual  
36 analogue scales for pain or overall health status. They may also report the time  
37 to first bowel movement or the time taken to return to normal activities. All such  
38 outcomes were recorded, along with the timing of the assessment.

## 39 **Results**

### 40 *Search results*

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42  
43 Our initial search retrieved 15771 results (fig 1.). After applying search filters  
44 [studies published between 1<sup>st</sup> January 1995 to 31<sup>st</sup> March 2016, human trials  
45 only, participants aged  $\geq 19$ , studies written in English], we excluded 9286  
46 studies, resulting in 6485 papers for our initial review. After screening the  
47 citation titles, we ultimately categorised 874 studies as 'definitely possible' or  
48 'uncertain'. This fell to 174 comparative studies after title and abstract screening.  
49 The full text of all 174 articles was assessed for details of study methodology.  
50 This identified 31 RCTs included in the present systematic review.  
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Figure 1. PRISMA diagram showing selection of RCTs for this review



### Study demographics

Study demographics and design characteristics are shown in Table 1. The 31 RCTs included 3,367 patients with a mean of 109 patients, range 24 to 337. One study[28] appears twice since it divided patients into simple and complex hernia groups, creating two individual trials (suture vs mesh repair and prosthetic mesh vs auto-dermal graft repair). Five RCTs were carried out in both the Netherlands[29–33] and Spain[34–38]. Thirteen RCTs were multi-centre and 18 were single centre. Over the past 20 years the number of RCTs performed increased, with 8 published between 1995 to 2005 versus 23 published from 2005 to 2016. There were 3 groups where RCTs compared the same

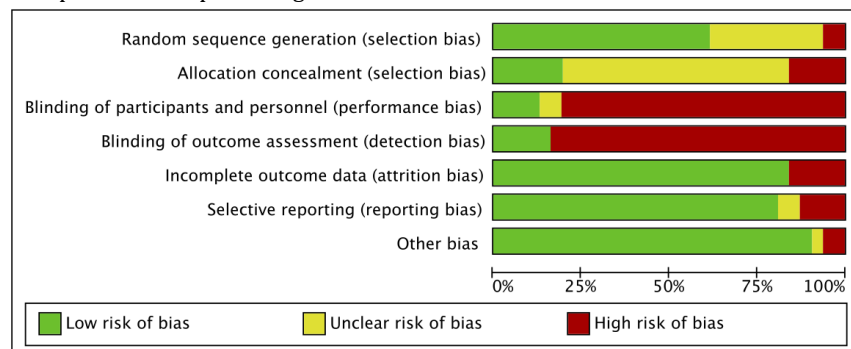
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interventions: Eleven studies compared laparoscopic versus open repair; 5 studies[28,30,36,39,40] compared suture versus mesh repair and 3 studies[37,41,42] compared tack versus suture mesh fixation in laparoscopic VH repair.

Table 1. Demographic and characteristics of the 31 RCTs included in the Systematic Review.

<b>Included Studies - Demographics</b>		
<b>Characteristic</b>	<b>Subgroup</b>	<b>No. of RCTs</b>
<b>-Country of Publication</b>	Netherlands[29-33] Spain[34-38]	5
	India[41-43] Egypt[44-46]	3
	Pakistan[40],[47] Turkey[39],[48] Italy[49,50]Germany [28],[51]	2
	Sweden[52] USA[53] Australia[54] Lithuania[55] France[56] Belgium[57] Denmark[58]	1
<b>-Multi vs Single-centre</b>	Multi centre[28-30],[32-34],[40],[49],[51-53],[57-58]	13
	Single centre[31],[35-39],[41-46],[48-50],[54-56]	18
<b>-Year of Publication</b>	1995-2005[28],[30],[32],[35-36],[39],[46]	7
	2006-2016[29],[31],[33-34],[37-38],[40-45],[47-58]	24
<b>Included Studies</b>		
<b>Characteristic</b>	<b>Subgroup</b>	<b>No. of RCTs</b>
<b>-Trial Groups</b>	Laparoscopic vs. Open[29],[34-35],[43],[47-50],[52-54]	11
	Open mesh vs. suture[28],[30],[36],[39-40]	5
	Laparoscopic mesh fixation; Tacks vs. Sutures[31],[37],[41-42]	3
	• Open VH repair:	
	<i>Onlay vs. Sublay</i> [44],[55]	2
	<i>Light weight vs. Heavy weight mesh</i> [32]	1
	<i>Medium weight vs. Medium weight mesh</i> [51]	1
	<i>Autograft vs. Prosthetic mesh</i> *[28*]	1
	<i>Component separation vs. Prosthetic mesh</i> [33]	1
	<i>Onlay vs. Underlay</i> [45]	1
	<i>Intraperitoneal vs. Onlay [bridging]</i> [46]	1
	<i>Ventral patch vs Biomesh composite mesh</i> [56]	1
	• Laparoscopic VH repair:	
	<i>Double crown tack vs. suture and tack mesh fixation</i> [31],[57]	2
	<i>Double crown tack vs. fibrin sealant mesh fixation</i> [58]	1
	<i>Light weight mesh vs. Medium weight mesh</i> [38]	1
	Total	32*
	*Large hernias from Korenkov et al. (a suture vs. mesh RCT) were analysed as a separate category. This makes this total 32 rather than 31.	
<b>-Hernia type</b>	Primary hernias only[36],[39-40],[44-45],[47]	6
	Incisional hernias only[28-30],[32-34],[38],[46],[49-53],[55]	14
	Primary and incisional hernias[31],[35],[37],[41-43],[48],[54],[56-58]	11
<b>-Primary outcomes</b>	Hernia recurrence[28],[49],[54],[56]	4
	Quality of life/ Health questionnaires[32],[34],[51-52]	4
	Pain [measured using visual analogue scores][29],[31],[57],[58]	4
	Pain and hernia recurrence [two primary outcomes][38]	1
	Mesh shrinkage[37]	1
	Total complications rates[53]	1
	Unclear[30],[33],[35-36],[39-48],[50],[55]	16
<b>-Risk of Bias: Cochrane Collaboration's tool</b>	High risk of bias[28-50],[52-58]	30
	Low risk of bias[51]	1

Figure 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.



### Risk of bias and study design

Thirty RCTs were assessed as at high risk of bias with just one[51] considered at low risk. Figure 2 shows that this high level of bias is mostly due to the failed blinding of trial participants, personnel (surgeons) and outpatient assessors. Only two trials[32],[51] achieved blinding for both these criteria.

### Hernia morphology

Twenty-three of 30 (76.6%) RCTs used hernia dimensions as an inclusion criteria and one RCT[28] divided hernias into simple and complex categories using a 10cm defect width cutpoint. Seven trials had no selection criteria that used hernia dimension. The exact nature of dimension inclusion criteria varied across trials, ranging from hernias with a width of less than 4cm[39], to hernias with a width of greater than 10cm[28,46]. Fourteen trials (45.2%) recorded the average defect surface area, which ranged from 3.4cm<sup>2</sup> to 141.2cm<sup>2</sup>, with a mean of 43.1cm<sup>2</sup>. Eleven trials (35.5%) recorded the average or median hernia width within each comparison group, which ranged from 3.6cm to 17cm with a mean of 7.5cm. None of the RCTs reported loss of domain or used loss of domain for patient selection (Table 2.).

As anticipated, no RCT recorded either VHWG grade or CDC wound classification of included hernias. Indeed, no RCT used a VH grading scale of any description. Six trials (19.3%) included primary VHs only, 14 trials (45.2%) included incisional hernias only, and 11 trials (35.5%) included both primary and incisional hernias. Ten of these 11 trials, including both primary and incisional VHs, reported the proportion of primary to incisional hernias, with a mean of 32 primary to 41 incisional hernias (range 31:7[58] to 18:65[57]). Seven of the 25 trials (28%) analysing incisional hernias included the ratio of primary incisional hernias to recurrent incisional hernias (mean of 84.1 primary to 28.3 incisional hernias, range 160:3[49] to 24:30[28]). Only two trials [30,47] reported the number of patients with previous ventral wound infection.

Table 2. Summarising the hernia morphology data reported.

<i>Hernia dimension</i>	<i>No. of RCTs reporting variable</i>
Average hernia defect surface area	14[30-31],[35],[37-38],[41],[43],[50],[52-57]
Average hernia defect width	11[28,29],[32-34],[38],[40],[44],[49-50],[52]
Loss of Domain	0

*Pre-operative patient characteristics and co-morbidities*

Table 3 summarises the patient characteristics and comorbidities reported. The pre-operative patient characteristics and comorbidities reported differed between trials. While many reported basic patient demographics of age, gender and BMI, few went beyond this to report patient comorbidities, including smoking status, diabetic status and steroid use.

Table 3. Preoperative patient characteristics and comorbidities reported.

<i>Patient characteristic/comorbidities</i>	<i>No. of RCTs reporting variable</i>
Age [mean]	30[28-39],[41-58]
Gender [male/female ratio]	29[28-39],[41-50],[52-58]
Obesity [as a ratio >/< 35 or mean [SD]]	23[28-34],[37-38],[41-45],[48-50],[51-53],[55-58]
No. patients ASA 3	10[29],[31],[36-37],[39],[45],[49],[51-53]
COPD	8[28],[34],[38],[43],[45],[51-53]
Smoking status	8[28],[30],[45],[51-53],[56-57]
No. patients with Diabetes	7[34],[38],[44],[51-53],[56]
No. patients ASA 1	7[29],[31],[45],[49],[51-53]
No. patients ASA 2	7[29],[31],[45],[49],[51-53]
SF-36 QoL questionnaire <sup>[59]</sup>	3[32],[51],[52]
No. patients using steroids	3[28],[51],[53]
No. of arteriopathies [IHD/PVD/CVA]	3[28],[44],[52]
No. patients ASA 4	3[29],[49],[51]
Average ASA score	2[34],[55]
Liver cirrhosis / Childs-Pugh A	1[44]
SF-12 QoL questionnaire <sup>[59]</sup>	1[56]

*Intra-operative variables*

Table 4 shows that intraoperative variables were reported with increased frequency compared to pre-operative variables and patient comorbidities. Mode of surgery, type of mesh implanted (prosthetic, composite, biosynthetic or biologic) and anatomical layer were recorded in all 31 RCTs. Operation duration, intra-operative blood loss and the experience of the principal operating surgeon were all reported less frequently.

Table 4. Intra-operative variables reported.

<b>Intra-operative variable</b>	<b>No. of RCTs reporting variable</b>
Mode of Surgery [laparoscopic/open]	31[28-58]
Category of mesh used	31[28-58]
Anatomical layer of mesh placement	31[28-58]
Duration of operation	27[28-31],[33-45],[48-50],[52-58]

Experience of the principal surgeon	14[29],[31],[33-34],[36],[46-47],[49],[52-55],[57-58]
Intra-operative blood loss	3[29],[33],[43]

### *Clinical outcomes*

Sixty-four different clinical outcomes were reported overall, with little consistency between trials, even when reporting similar intervention groups and primary outcomes. Indeed, 16 (51.6%) RCTs stated no primary outcome explicitly (Table 1). Of the 15 RCTs (48.4%) stating a primary outcome; 4[28,49,54,56] used hernia recurrence and 4[32,34,51,52] employed quality of life. Three trials[32],[51,52] used the SF-36 questionnaire[59] and 1 trial[34] used the EQ-5D questionnaire[60]. Four trials[29,31,57,58] used pain as their primary outcome, assessed via visual analogue scales (VASs). One trial stated both pain and recurrence as two separate primary outcomes, with no statistical accounting for co-primary outcomes[38]. The remaining two trials used mesh shrinkage[37] or standardised complication rates[53] as their primary outcomes respectively. Multiple different primary outcomes led to many different clinical and patient reported outcomes (as shown in online resource 2).

Length of follow-up was reported in all studies and averaged 24.5 months (range 1 month to 64 months). Fifteen of 31 (48%) trials had follow-up of at least 24 months. One trial[52] did not report hernia recurrence rate. Of the 30 trials reporting hernia recurrence, 1 RCT[36] reported recurrence at 5 years post repair, 4 RCTs[29-30],[41],[56] reported recurrence at 3 years, 15 RCTs at 2 years, 13 RCTs at 1 year, 5 RCTs[37],[41],[43],[50-51] at 6 months and 1 RCT[34] at 3 months. Six (20%) of 30 RCTs defined recurrence: definitions are shown in table 5. Only three trials used the same definition. Eight (29%) of 30 trials did not specify the method used to detect recurrence. Twelve trials (43%) used clinical examination alone to detect recurrence. Ten (33%) trials used imaging if recurrence was in doubt, or to confirm a recurrence suspected clinically. Five (50%) of these 10 trials[29,31,33,43,57] used either CT or USS to detect recurrence, 3 (30%) trials[30,42,58] used USS alone and 2 (20%) trials[38,46] used CT alone. Recurrence rates increased when imaging was used. Trials using clinical examination had a 4% median recurrence rate whereas trials using USS or CT, USS alone, or CT alone had median recurrence rates of 7%, 9% and 7% respectively. Trials that did not specify test methods for recurrence had a mean re-herniation rate of 7%. The method used to detect hernia recurrence did not depend on the size or type of hernia included in the trial (as shown in online resource 3). Patient reported outcomes used the SF-36[59], SF-12[59], EQ-5D[60], and GIQL[62] questionnaires as well as VASs, to assess pain and overall health status. These were also carried out at varying time intervals. The Calvien-Dindo[61] scale for post-operative complications was used in 9 of the trials to classify complication severity.

Table 5. Six definitions of hernia recurrence encountered in the systematic review.

Reference:	Definition
Arroyo et al.[36] (2001)	'the presence of a defect on the central part of the midline aponeurosis around the umbilicus, where the operation had been performed

Bensaadi et al.[56] (2014)	previously. 'a defect of the midline aponeurosis around the umbilicus at the site where the operation was performed.'
Lal et al.[40] (2012)	'the presence of a defect on the central part of the midline aponeurosis where the operation had been performed previously.'
Luijendijk et al.[30] (2000)	'any fascial defect that was palpable or detected by ultrasound examination and was located within 7cm of the site of hernia repair.'
Pring et al.[54] (2008)	'a clinically detectable defect, associated with the protrusion of viscera on straining.'
Muysoms et al.[57] (2013)	'Patients were considered free from recurrence if at clinical examination, no hernia was felt in an upright position during valsalva manoeuver.'

## Discussion

This systematic review has analysed the reported perioperative variables and postoperative outcomes from randomised controlled trials of elective VH repair, performed over the last twenty years. Important findings include the general absence of: a standardised pre-operative patient variable dataset; a universally accepted definition of recurrence; standardised test methods to detect recurrence; standardised assessment times for the key primary and secondary outcomes, and standardised evaluation tools for post-operative pain and quality of life. This lack of standardisation limits the validity of trial comparisons made by meta-analyses and comparison of trials by practicing surgeons. Our review provides evidence-based justification for urgent investment in a core perioperative and clinical outcome dataset applicable to trials of VH surgery. This should be developed and validated with key stakeholders to improve the quality of outcome reporting in this rapidly developing field. A group such as COMET needs identification and encouragement to help develop and endorse this work[63].

As VH research evolves, academics are searching increasingly for outcome predictors. Potentially reliable predictors can be identified from the primary literature only when they are reported. Our review has found that randomised controlled trials are focusing on surgical technique and failing to report variables that would normally be regarded as important predictors. For example, many pre-operative patient comorbidities and, in particular, measures of hernia morphology (e.g. hernia width and area) were omitted from most reports. Loss of domain was not reported by any trial. Because current evidence is contradictory, with some studies suggesting that hernia width does correlate with recurrence[64] whereas others do not[65,66], future trials need to report apparently important predictors to facilitate subsequent analysis. Investigators should also grade hernias using appropriate scales, for example the VHWG scale[17] and the CDC wound classification scale[27] as these scales themselves may prove to be outcome predictors. Our review demonstrates that a trial dataset with multiple pre-operative patient variables (diabetes, COPD, BMI, hernia grade etc), including pre-operative CT scan dimensions (hernia defect area, hernia width, loss of domain etc) and intra-operative variables (operation



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7 time, anatomical plane of mesh insertion, reconstructive technique etc) is  
8 required.

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10 While 8 of the 30 trials (26.7%) reporting hernia recurrence didn't even define  
11 how recurrence was detected, the remaining trials used differing recurrence  
12 detection methods ranging from undefined clinical examination to undefined  
13 imaging methods. This introduces bias depending on the differing examination  
14 and imaging methods used. There was much variation in the timing of  
15 assessment for hernia recurrence. This observed lack of consensus regarding  
16 assessment timing, test methods for recurrence, and definitions of recurrence  
17 limits data availability and consistency, and impairs meta-analysis. To achieve  
18 standardisation a clear definition of VH recurrence is required. Imaging is likely  
19 the most precise method with which to determine recurrence, but a radiological  
20 definition of recurrence is required that incorporates measures of clinically  
21 important and unimportant reherniation. Currently, there is considerable  
22 variability in recurrence reporting for CT scans[67]. Our review suggests that the  
23 use of imaging does increase reported recurrence rates, which would be  
24 anticipated since subclinical recurrences will be identified.

25 RCT dataset designers should also consult the recommendations made by  
26 Muysoms et al. following a consensus meeting in Palermo, Italy in 2012[68]. This  
27 work gives detailed advice on how to carry out statistically sound research  
28 (interventional studies, observational studies, systematic review, and meta-  
29 analysis) in abdominal wall repair. Of particular relevance, this article advises  
30 using the EuraHS definition for hernia recurrence[69]; *"a protrusion of the*  
31 *contents of the abdominal cavity or preperitoneal fat through a defect in the*  
32 *abdominal wall at the site of a previous repair of an abdominal wall hernia"*, which  
33 we support, although (as stated above) a future definition of recurrence that  
34 includes radiological detection maybe more accurate but requires development.  
35 Muysoms et al. recommend using the EHS hernias classifications scales and  
36 measuring post-operative complications using the Clavien-Dindo classification  
37 system but do not define or list any other peri-operative or post-operative  
38 outcome variables that sound be measured. Importantly, they do allow for  
39 variability in the method used for recurrence detection and the time to  
40 outpatient assessment, which we feel this should be standardised, especially in  
41 RCTs. To standardise trial outcomes, a dataset with clear definitions and follow  
42 up assessment times is warranted.

43 A standardised dataset should include tools to assess chronic pain and quality of  
44 life (QoL). When comparing different surgical techniques, chronic pain and QoL  
45 are important patient-centred endpoints, as patients frequently place more  
46 emphasis on these outcomes than the operative surgeon. In this review, simple  
47 visual analogue scales were used commonly to assess pain. However, these  
48 analogue scales, and the timings of assessment were not standardised. A future  
49 dataset must standardise pain assessment. QoL was measured using many  
50 different questionnaires (SF-36[59], SF-12[59], EuroQoL[60] and GIQL[62]).  
51 These questionnaires are commonly used and they allow for health economic  
52 analysis across different disease states. However, they are not disease specific,  
53 and may miss important patient reported outcomes specific to hernia surgery.

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7 Due to the unique set of complications arising from VH surgery, the importance  
8 of chronic pain and QoL, a hernia-specific patient reported outcome assessment  
9 tool, such as the Carolinas Comfort Scale[70] or the EuraHS-QoL  
10 questionnaire[69], should be used.

11  
12 When constructing a VH perioperative variable and postoperative outcome  
13 dataset for randomised control trials, workers should also consult the VH  
14 databases currently being used in America[71], Europe[69], Denmark[72] and  
15 Spain[73]. These databases collect data prospectively from large cohorts of  
16 patients and will generate sizeable observational studies. These databases have  
17 been constructed by VH experts with multiple peri-operative and post-operative  
18 data-points, many of which should be included in an RCT dataset.

19  
20 As well as focusing on standardised definitions and datasets, academic surgeons  
21 carrying out RCTs should make concerted efforts to reduce trial bias. Thirty of  
22 the 31 included trials were assessed as at high risk of bias. Many of the included  
23 trials performed poorly in 3 out of the 7 domains of the Cochrane Collaboration's  
24 tool for risk of bias[26]. Many trials failed to specify how participant group  
25 allocation was concealed, failed to blind participant and surgeon from the  
26 allocated treatment, and there was no blinding in the outpatient assessment  
27 clinic. Traditionally, surgical trials are usually at high risk of bias due to the  
28 impossibility of blinding the primary surgeon. However, if visible skin changes to  
29 the participant do not differ between the treatment groups [e.g. open VH repair  
30 with onlay vs. sublay mesh], it is possible to blind both the participant and an  
31 independent assessor. In addition, concealment of treatment allocation should  
32 follow the standards set by the Cochrane Collaboration. In surgery, the allocated  
33 treatment should only be revealed to an independent surgeon after the  
34 participant is under general anaesthetic and after the participant has been  
35 consented to take part in the trial and both possible treatments.

36  
37 Further bias can arise in RCTs due to commercial funding and readers should be  
38 aware of this. We accept there are difficulties in achieving non-commercial  
39 funding for RCTs in hernia research and that without proper funding scrupulous  
40 methodology can be challenging due to the high work load. Eight out of 31 one of  
41 the trials received commercial funding[31,32],[37],[51],[54],[56-58], one trial  
42 received non-commercial funding[53] and one trial received both commercial  
43 and non-commercial funding[52]. In the remaining 21 trials the funding method  
44 was not specified. The practical difficulty of obtaining non-commercial funding  
45 can only be addressed by researchers, who whilst applying for funding must  
46 clearly explain the technical difficulties faced by reconstructive surgeons and the  
47 high prevalence of morbidity suffered by patients after hernia repair; namely  
48 chronic pain and recurrence. If researchers face difficulties with funding or  
49 carryout research with commercial funding, little can be done apart from  
50 carrying out research to highest possible standards. We note that any data is  
51 better than no data, as supported by Lilford et al[74].

## 52 **Conclusion**

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7 So far systematic reviews of elective VH RCTs have focused on comparing the  
8 outcomes of open versus laparoscopic VH repair[75],[76],[77]. This review is the  
9 first to assesses the methodology of VH RCTs. The results show that the  
10 perioperative variables and postoperative outcomes reported by RCTs of VH  
11 repair lack definition and consistency. To solve this, a defined minimum dataset  
12 of variables and outcomes is required. Since operative success is determined by  
13 the presence or absence of hernia recurrence, recurrence is therefore the prime  
14 outcome and requires standard clinical and radiological definitions, together  
15 with a minimum period of follow-up. For a clinical definition, we recommend  
16 using the European definition for hernia recurrence[69], and that a radiological  
17 definition requires development. Such measures will standardise and therefore  
18 improve outcome reporting in this rapidly expanding and important field,  
19 increasing data homogeneity and the value of subsequent meta-analysis.

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Figure 1. PRISMA diagram showing selection of RCTs for this review

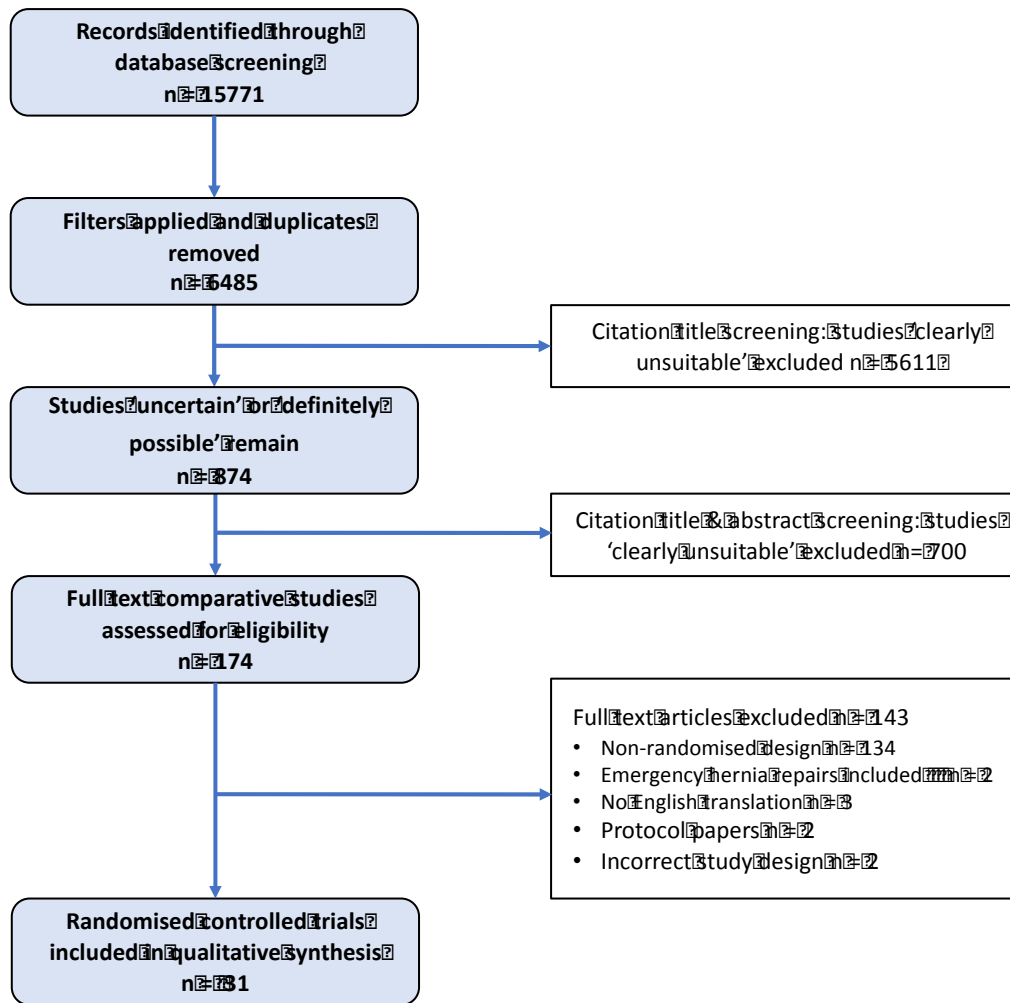


Figure 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

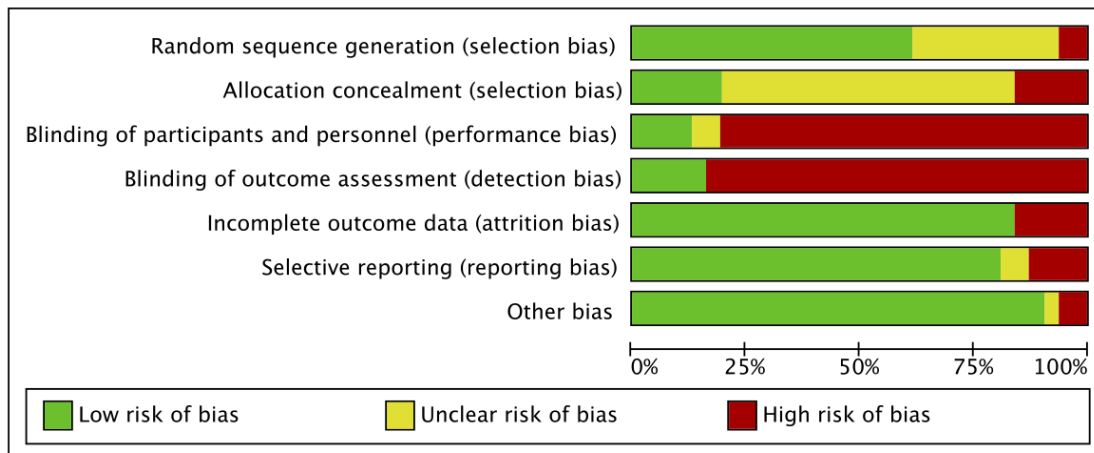


Table 1. Demographic and characteristics of the 31 RCTs included in the Systematic Review.

<b>Included Studies - Demographics</b>		
<b>Characteristic</b>	<b>Subgroup</b>	<b>No. of RCTs</b>
<b>-Country of Publication</b>	Netherlands[29-33] Spain[34-38]	5
	India[41-43] Egypt[44-46]	3
	Pakistan[40],[47] Turkey[39],[48] Italy[49,50]Germany [28],[51]	2
	Sweden[52] USA[53] Australia[54] Lithuania[55] France[56] Belgium[57] Denmark[58]	1
<b>-Multi vs Single-centre</b>	Multi centre[28-30],[32-34],[40],[49],[51-53],[57-58]	13
	Single centre[31],[35-39],[41-46],[48-50],[54-56]	18
<b>-Year of Publication</b>	1995-2005[28],[30],[32],[35-36],[39],[46]	7
	2006-2016[29],[31],[33-34],[37-38],[40-45],[47-58]	24
<b>Included Studies</b>		
<b>Characteristic</b>	<b>Subgroup</b>	<b>No. of RCTs</b>
<b>-Trial Groups</b>	Laparoscopic vs. Open[29],[34-35],[43],[47-50],[52-54]	11
	Open mesh vs. suture[28],[30],[36],[39-40]	5
	Laparoscopic mesh fixation; Tacks vs. Sutures[31],[37],[41-42]	3
	• Open ventral hernia repair:	
	<i>Onlay vs. Sublay</i> [44],[55]	2
	<i>Light weight vs. Heavy weight mesh</i> [32]	1
	<i>Medium weight vs. Medium weight mesh</i> [51]	1
	<i>Autograft vs. Prosthetic mesh*</i> [28*]	1
	<i>Component separation vs. Prosthetic mesh</i> [33]	1
	<i>Onlay vs. Underlay</i> [45]	1
	<i>Intraperitoneal vs. Onlay [bridging]</i> [46]	1
	<i>Ventral patch vs Biomesh composite mesh</i> [56]	1
	• Laparoscopic ventral hernia repair:	
	<i>Double crown tack vs. suture and tack mesh fixation</i> [31],[57]	2
	<i>Double crown tack vs. fibrin sealant mesh fixation</i> [58]	1
	<i>Light weight mesh vs. Medium weight mesh</i> [38]	1
	Total	32*
	*Large hernias from Korenkov et al. (a suture vs. mesh RCT) were analysed as a separate category. This makes this total 32 rather than 31.	
<b>-Hernia type</b>	Primary hernias only[36],[39-40],[44-45],[47]	6
	Incisional hernias only[28-30],[32-34],[38],[46],[49-53],[55]	14
	Primary and incisional hernias[31],[35],[37],[41-43],[48],[54],[56-58]	11
<b>-Primary outcomes</b>	Hernia recurrence[28],[49],[54],[56]	4
	Quality of life/ Health questionnaires[32],[34],[51-52],	4
	Pain [measured using visual analogue scores][29],[31],[57],[58]	4
	Pain and hernia recurrence [two primary outcomes][38]	1
	Mesh shrinkage[37]	1
	Total complications rates[53]	1
	Unclear[30],[33],[35-36],[39-48],[50],[55]	16

<b>-Risk of Bias: Cochrane Collaboration's tool</b>	High risk of bias[28-50],[52-58]	30
	Low risk of bias[51]	1

Table 2. Summarising the hernia morphology data reported.

<b>Hernia dimension</b>	<b>No. of RCTs reporting variable</b>
Average hernia defect surface area	14[30-31],[35],[37-38],[41],[43],[50],[52-57]
Average hernia defect width	11[28,29],[32-34],[38],[40],[44],[49-50],[52]
Loss of Domain	0

Table 3. Preoperative patient characteristics and comorbidities reported.

<b>Patient characteristic/comorbidities</b>	<b>No. of RCTs reporting variable</b>
Age [mean]	30[28-39],[41-58]
Gender [male/female ratio]	29[28-39],[41-50],[52-58]
Obesity [as a ratio >/< 35 or mean [SD]]	23[28-34],[37-38],[41-45],[48-50],[51-53],[55-58]
No. patients ASA 3	10[29],[31],[36-37],[39],[45],[49],[51-53]
COPD	8[28],[34],[38],[43],[45],[51-53]
Smoking status	8[28],[30],[45],[51-53],[56-57]
No. patients with Diabetes	7[34],[38],[44],[51-53],[56]
No. patients ASA 1	7[29],[31],[45],[49],[51-53]
No. patients ASA 2	7[29],[31],[45],[49],[51-53]
SF-36 QoL questionnaire <sup>[59]</sup>	3[32],[51],[52]
No. patients using steroids	3[28],[51],[53]
No. of arteriopathies [IHD/PVD/CVA]	3[28],[44],[52]
No. patients ASA 4	3[29],[49],[51]
Average ASA score	2[34],[55]
Liver cirrhosis / Childs-Pugh A	1[44]
SF-12 QoL questionnaire <sup>[59]</sup>	1[56]

Table 4. Intra-operative variables reported.

<b>Intra-operative variable</b>	<b>No. of RCTs reporting variable</b>
Mode of Surgery [laparoscopic/open]	31[28-58]
Category of mesh used	31[28-58]
Anatomical layer of mesh placement	31[28-58]
Duration of operation	27[28-31],[33-45],[48-50],[52-58]
Experience of the principal surgeon	14[29],[31],[33-34],[36],[46-47],[49],[52-55],[57-58]
Intra-operative blood loss	3[29],[33],[43]

Table 5. Six definitions of hernia recurrence encountered in the systematic review.

Reference:	Definition
Arroyo et al.[36]	'the presence of a defect on the central part of the midline aponeurosis around the umbilicus, where the operation had been performed previously.'
Bensaadi et al.[56]	'a defect of the midline aponeurosis around the umbilicus at the site where the operation was performed.'
Lal et al.[40]	'the presence of a defect on the central part of the midline aponeurosis where the operation had been performed previously.'
Luijendijk et al.[30]	'any fascial defect that was palpable or detected by ultrasound examination and was located within 7cm of the site of hernia repair.'
Pring et al.[54]	'a clinically detectable defect, associated with the protrusion of viscera on straining'.
Muysoms et al.[57]	'Patients were considered free from recurrence if at clinical examination, no hernia was felt in an upright position during valsalva manoeuver.'





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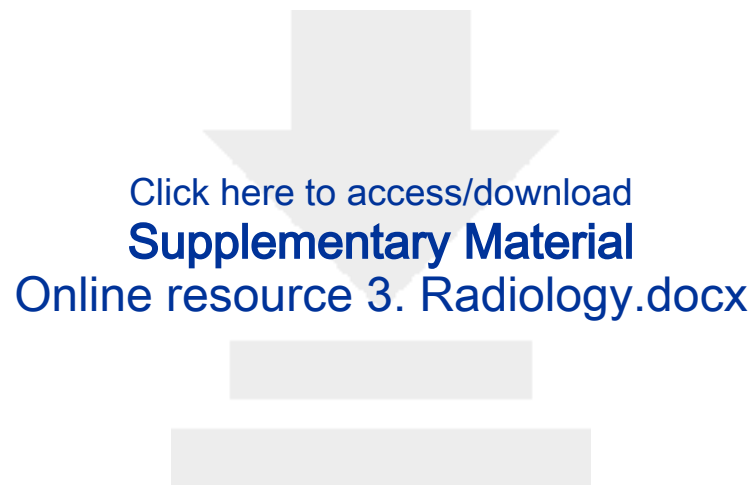
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