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The Experimental Methodology and Comparators Used for *In Vivo* Hernia Mesh Testing: A Protocol for Scoping Review

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Thomas Whitehead-Clarke[*1], Samuel Parker[2], Veronica Parisi[3], Alastair Windsor[4], Vivek Mudera[5], Alvena Kureshi[6]

[1]Division of Surgery and interventional science, University College London, Charles Bell House, Foley Street, London, W1W 7TY
[2]University college London Hospital, London, NW1 2BU
[3]University College London, WC1E 6BT
[4]Princess Grace Hospital, London, W1U 5NY
[5]Division of Surgery an Interventional science, University College London, WC1E 6BT
[6]Division of Surgery and Interventional Science, University College London, WC1E 6BT

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ABSTRACT

We present a protocol for a 10-year scoping review of methodology and comparators used for *in vivo* mesh testing. Our protocol has been developed in line with guidance from PRISMA. Our review will assess all literature from the last 10 years that has tested hernia mesh *in vivo* for mechanical, structural, or cellular properties. A bespoke literature search has been designed by a specialist science librarian and papers will be included or excluded using strict criteria. Our scoping review is not eligible for registration with PROSPERO.

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Contributions – TWC is the Guarantor. TWC and SP designed the inclusion/exclusion criteria. TWC and VP designed the search strategy. All Authors helped to draft the manuscript and approved the final version.

ADMINISTRATIVE INFORMATION

1 Title

a: Identification – The experimental methodology and comparators used for *in vivo* hernia mesh testing: a protocol for scoping review.

b: Update – This is the original review protocol; there are no updates to declare.

2 Registration

This scoping review is unregistered as it does not meet the inclusion criteria for registration through PROSPERO.

3 Authors

Contacts –

Mr Thomas Whitehead-Clarke (corresponding author)
Division of Surgery and Interventional Science
University College London
t.whitehead-clarke@nhs.net
Charles Bell House
Foley Street
London
W1W 7TY

Mr Samuel Parker
University College London Hospital

Ms Veronica Parisi
University College London

Professor Vivek Mudera
Division of Surgery and Interventional Science
University College London

Mr Alastair Windsor
Princess Grace Hospital
HCA healthcare

Dr Alvena Kureshi
Division of Surgery and Interventional Science
University College London

4 Amendments:

This is the first draft of our review protocol, and as such, no amendments are to be declared. In the event of any amendments, the date of each amendment will accompany a description of the change and its rationale.

5 Support:

a: Sources – This review has been supported financially by the British Hernia Society (BHS) as well as an independent research fund held by University College London Hospital (UCLH) Charity. It has received technical support from Library services at University College London (UCL).

b: Sponsor – The Division of Surgery and Interventional Science - University College London (UCL) is the sponsor meaning it has overall control of the data.

c: Role of sponsor or funder – The funders have supplied financial support to a postgraduate student to develop this research. Library services at UCL have contributed to the data search strategy. AK is an academic supervisor from the Division of Surgery and Interventional Science and has helped to draft the final protocol.

INTRODUCTION

6 Rationale:

100,000 abdominal wall hernias are repaired surgically in the UK each year (1). The vast majority are repaired using mesh implants, which have been proven to strengthen the repair

and reduce the chance of hernia recurrence (2). Before clinical use, mesh implants are tested on animals to prove their efficacy and biocompatibility. Meshes are implanted surgically into these animals under general anaesthetic and left *in situ* for several weeks. These animals are then euthanized and the mesh and surrounding tissue are explanted from each animal. The mechanical and histological properties of these samples are evaluated using various tests.

The methodology for these pre-clinical tests can vary significantly. A mixture of mechanical, immunochemical, and histological tests are often used in different combinations to test the efficacy and biocompatibility of hernia mesh. Different authors have highlighted the heterogeneity in the field, stating that techniques are so disparate that comparison is extremely difficult, and guidelines should be devised. (3, 4)

We will use this scoping review to assess and then document the current state of *in vivo* mesh testing and the variation in its practice. Whilst both clinicians and mesh developers would recognize the current variety in mesh testing, we believe this would benefit from methodological review and publication.

7 Objectives

This scoping review aims to summarise and analyse the methods used for *in vivo* pre-clinical testing of hernia mesh. For each study, the techniques used throughout the mesh testing process will be assessed. These include details of mesh implantation and sample explantation as well as testing methods and whether data is measured qualitatively or quantitatively.

Participants: We will review all indexed papers that use *in vivo* models to test the properties of surgical mesh used for hernia repair. Papers can analyse new or existing mesh in a single arm or comparative study.

Interventions: The review will document the range of experimental variation at each stage of the mesh testing process. Interventions will be described as follows:

Implantation/ explantation techniques:

Methods used for the implantation and explantation of the mesh and mesh/tissue sample will be reviewed. This will assess the species of animals used in each study as well as the defect (if any) created in the animal's abdominal wall to simulate a hernia. We will also gather information about mesh placement techniques and methodology for mesh/tissue sample explantation.

Testing techniques:

- *Mechanical properties:* We will review how the tissue/ mesh sample is tested mechanically. This will include not only the method but also how results are summarized.

- *Structural properties*: We will look at how the structure of the mesh/tissue sample is analysed. This will once again include methods used to view the ultrastructure, and how that data is summarized.

- *Inflammatory cellular properties*: We will review how studies assess inflammation and cell behaviour in the mesh/tissue sample. Again, both methodology and type of data output will be looked at.

Comparators: Comparators for each study will take the form of either the absence of mesh or a different mesh type. Because the review will include single-arm studies, comparators may be absent for some studies. This review is focused on testing methods and as such comparators are not relevant to our outcomes.

Outcomes: The scoping review will produce a detailed summary of the current techniques used for *in vivo* mesh testing. It will allow us to look at the most frequently used techniques, the variety in practice as well as the presence, or lack, of standardisation.

Specific data points to be captured will be described in section 12 of this protocol.

METHODS

8 Eligibility Criteria:

We will conduct a literature search of the Embase and Medline databases using the OVID interface. Once a list of publications is obtained, studies will be included/excluded according to the criteria below:

Inclusion Criteria:

- Single-arm studies and comparative studies that look to test the effectiveness and/or biocompatibility of surgical mesh.

- *In vivo* studies where the mesh and tissue sample has been explanted from the animal before testing.

- Studies looking at any type of mesh or mesh with a new coating. This includes synthetic, biological, or composite meshes.

- Studies that examine mesh/ tissue interaction at the abdominal wall for Inflammatory, structural or biomechanical properties.

- Studies where the mesh is implanted in the abdominal wall. This can include any specific mesh placement including anything from on-lay to intraperitoneal placement.

- Studies published between January 2009 and October 2019 inclusive.

- Studies published in the English language.

Exclusion criteria will include:

- Studies that compare or assess fixation technique.

- Studies where the primary subject of the investigation is not meshed performance.

- Studies where a mesh or coating is exclusively assessed for adhesion formation or mesh shrinkage.

- Studies testing new pharmacological products.

- *In vitro* studies.

- Studies where the mesh is placed and assessed for femoral/obturator hernias.

- Studies where the mesh is placed around pelvic organs to test use in treatment for prolapse/incontinence.

- Studies where the mesh is used as part of a rectopexy procedure for prolapse surgery.

9 Information Sources:

A literature search strategy has been developed using medical Subject headings (MeSH) and text words specific to hernia mesh and *in vivo* testing. We will conduct a literature search of both the Embase (OVID Interface 1980 onwards) and MEDLINE (Ovid Interface 1948 onwards) databases. The search will be limited to the English Language and from Jan 1^{st,} 2010 to Oct 1^{st,} 2019.

10 Search Strategy:

The search strategy has been developed by TWC and VP. VP provides expertise as the science librarian for University College London. The search is limited between 1st January 2010 and the 1st of October 2019. The search will be limited to studies in the English language.

Studies will be identified from two separate search engines (Medline and Embase) through the OVID interface. Different strategies have been designed for each database, these are outlined below:

Medline

1. hernia, abdominal/ or hernia, inguinal/ or exp hernia, ventral/ or incisional hernia/

2. ((abdominal or incisional or Ventral or inguinal or postoperative or parastomal or umbilical) adj3 hernia*).tw.

3. 1 or 2

4. Surgical Mesh/

5. mesh*.tw.

6. 4 or 5

7. Materials Testing/

8. test*.tw.

9. assess*.tw.

10. compar*.tw.

11. measur*.tw.

12. or/7-11

13. 3 and 6 and 12

14. limit 13 to animals

15. limit 14 to (English language and yr="2009 -Current")

Embase

1. abdominal wall hernia/ or inguinal hernia/ or parastomal hernia/ or spigelian hernia/ or umbilical hernia/

2. incisional hernia/

3. ((abdominal or incisional or ventral or inguinal or postoperative or post-operative or parastomal or umbilical) adj3 hernia*).tw.

4. 1 or 2 or 3

5. surgical mesh/ or mesh plug/ or nonabsorbable mesh/ or titanium mesh/ or transabdominal mesh/

6. mesh*.tw.

7. 5 or 6

8. materials testing/

9. test*.tw.

10. assess*.tw.

11. compar*.tw.

12. measur*.tw.

13. 8 or 9 or 10 or 11 or 12

14. 4 and 7 and 13

15. limit 14 to animals

16. limit 15 to (English language and yr="2009 -Current")

11 Study Records

A Data management – Literature search results will be uploaded onto Covidence (Covidence systematic review software Veritas Health Innovation, Melbourne, Australia, www.covidence.org.) an online systematic review software. This platform will be used for the selection of relevant papers. Once papers have been selected, standardized forms will be created using Microsoft Excel (Microsoft Corporation. (2018). *Microsoft Excel*. Retrieved from https://office.microsoft.com/excel) for data extraction.

B Selection process – Literature search results will be uploaded onto Covidence. Four separate reviewers will assess an equal share of the papers for inclusion. Titles and abstracts will be screened for selection through inclusion/exclusion criteria. In cases of uncertainty, these will be resolved through discussion, with senior authors having decisive input. Reviewers will not be blinded to study author or journal-title.

C Data collection process- Using a standardized form on Microsoft Excel, four reviewers will independently extract data from an equal share of the articles included. To ensure consistency, a collaboration exercise will be performed before data collection, after each reviewer has extracted data from 3 papers. This exercise will help standardize the process between reviewers. Because of the nature of the review, the data entry form may need to be altered during data collection. There will, therefore, be meetings between reviewers every 2-3 weeks to discuss issues with data entry. Uncertainty will be resolved by discussion amongst senior authors.

12 Data Items:

Data points for extraction have been mapped to our objectives in section 7. We will gather the following specific data points from each article:

Study/ experimental data:

- Primary outcome/ variable assessed
- Animal Species Used
- Animal subspecies
- Average Weight

- Average Age
- Defect shape (e.g linear or 2-dimensional)
- Defect depth
- Defect size
- Mesh size
- Mesh placement (the plane of the abdominal wall)
- Defect closure
- Attachment of Mesh (Sutures/no sutures etc)
- Times of mesh explantation (single Vs Multiple)

Testing techniques:

Mechanical properties:

- Method of testing used.
- The scale used to quantify/ qualify mechanical strength
- Initial load on testing mechanism.
- Speed (or rate of increase) of test mechanism
- Width of tensile test strips.
- Distance between clamps.
- The cross-sectional area of testing strips.

Structural properties:

- The technique used to visualize collagen.
- Differentiation of type 1 from type III collagen
- The scale used to quantify/ qualify presence of collagen.

- Other structural components assessed (tissue integration, fibrous encapsulation, etc).

- The scale used to quantify /qualify other structural components.

Cell behaviour:

- Types of cell visualized/ counted

- The technique used to visualize each type of cell.

- The scale used to quantify/ qualify presence of cells.

13. Outcomes and prioritization:

Our review is a scoping review rather than a systematic review. As a result, there are no outcome measures beyond the testing methods used. We are not hoping to assess which meshes have superior performance.

14. Risk of bias in individual studies:

Our scoping review is exclusively focused on summarising the testing methods used for *in vivo* or pre-clinical hernia mesh testing. The results of these studies are not the subject of this review, and therefore bias between studies will not be assessed.

15. Data synthesis:

A – The data being collected will not be quantitatively synthesized.

B – The data being collected will not be quantitatively synthesized.

C – Our data is not suitable for any other analysis.

D – A systematic narrative synthesis will be provided with the information presented in the text and tables to summarise and explain the characteristics and findings of the included studies.

16. Meta- Bias –

Our scoping review is exclusively focused on summarising the testing methods used for *in vivo* or pre-clinical hernia mesh testing. The results of these studies are not the subject of this review, and therefore bias between studies will not be assessed.

17. Confidence in cumulative evidence.

Our review is a scoping rather than a systematic review. We will not be looking to assess the strength of our evidence, as there is no single scientific question being asked.

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Image *Author -1*	***Mr Thomas Whitehead-Clarke – Corresponding Author*** *University College London* *Charles Bell House* *Foley Street* *London* W1W 7TY
Image *Author -2*	***Mr Samuel Parker*** *University College London Hospital*
Image *Author -3*	***Ms Veronica Parisi*** *University College London*
Image *Author -4*	***Prof Vivek Mudera*** *University College London*
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