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The NIHR Evaluation, Trials and Studies Coordinating Centre (NETSCC), based at the University of Southampton, manages evaluation research programmes and activities for the NIHR

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HTA no 14/151: Use of fibrin sealant during surgery

FINAL PROTOCOL

May 2015

1. Title of the project

The use of fibrin sealant during non-emergency surgery: a systematic review of randomised controlled trials and observational studies

2. Name of External Assessment Group (EAG) and project lead

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3. Plain English Summary

Fibrin sealants (FS) are used by surgeons during a variety of operative procedures at many sites including, the liver, breast, pancreas, thoracic and neurosurgical procedures. They are used to seal tissues, and prevent the accumulation of post-operative fluid and blood loss. Aerosol sprays, sponges, bandages and pad preparations are available and all contain elements that make blood clot and help the body repair.

After surgery the body's natural response to the removal of organs or tissues is to fill the space with fluid and blood cells. During this process a collection of fluid and cells can result in the formation of a seroma (collection of clear yellow fluid). There are some parts of the body that are especially prone to seromas, e.g. the breasts, and parts of the digestive tract. These can cause problems because they can become infected or leak fluid and, if they remain, over time become swollen, hard and uncomfortable. Occasionally the only way to cure the problem is to have more surgery to remove the seroma or have it drained with a fine needle, which might increase the time spent in hospital.

To try to stop seroma forming, surgeons sometimes leave a drain (tube) in the wound to make sure fluid can escape and does not build up after the operation. After thoracic surgery the placement of a post-surgical drain can increase length of hospital stays and cause discomfort. Problems arise when the drains do not always work properly and can become blocked and infected. Fibrin sealants have been found to stop fluid collecting in the body after operations but it is not clear if this "good effect" works for all types of operations. There is concern that some types of fibrin sealants can have bad effects, such as leaving pockets of air in the body which can be dangerous.

The aim of this review is to find out what research has been done to evaluate the use of fibrin sealants in non-emergency surgery in adults treated in hospitals and to identify whether their use shows any benefits or harms.

4. Decision problem

FS are commercial products which usually comprise two substances which occur naturally in mammals: fibrinogen, a protein and thrombin, an enzyme which acts on fibrinogen to produce a fibrin clot, exactly as it occurs in normal blood clotting. The components used in these products are derived from either human or animal blood. There are different preparations of FS; patches, sponges or bandage formulations which can all be impregnated with fibrinogen and thrombin. Alternatively, fibrin glue (FG) is a mixture of the two substances in liquid form which is dispensed via a "gun" and there is also a liquid "droplet" formulation which is delivered in an aerosol spray.[1, 2] FS are used during surgical procedures in many sites of the body and are widely regarded as useful adjuncts to aid

haemostasis and reduce seroma formation.

Arrest of Haemorrhage

Assisting the arrest of haemorrhage (haemostasis) peri-operatively is an important function of fibrin sealant preparations. Their use during the removal of uterine fibroids in premenopausal women has been shown to reduce blood loss and consequently the rate of blood transfusions. However the quality of evidence was assessed to be low.[3] This effect was also reported in a systematic review of surgical interventions for liver, orthopaedic, vascular, prostate, thoracic, renal, pancreatic and cardiac conditions. A randomised controlled trial evaluating the use of FS in total knee arthroplasty procedures also demonstrated statistically significant reductions in patient blood loss.[1, 4, 5]

Tissue Adhesion or Sealing

A systematic review summarised the evidence for FG in the repair of pilonidal disease (the invasion of hair into the skin of the natal cleft). The review included 5 trials in which FG was used to fill dead space and sinus tracks during surgery. While the reviewers report equivalent or better reported healing times at an average of 2–6 weeks and low recurrence rates between 0 and 17% at follow-up periods between 4 and 28 months for all patients treated with FG compared with conventional therapies, no statistical significance between those who received FG and those who did not was observed.[6]

Hernia Repair

A systematic review of randomised and non-randomised studies evaluating FS used in the surgical management of hernia repair concluded FS are an effective alternative to mechanical approaches.[7]

Dural repair in neurosurgery

FS can be used as an adjunct to dura (the outer most layer of the brain and spinal cord) repair to achieve intra-operative watertight closure of the dura and reduce post-operative cerebrospinal fluid leak. A randomised controlled trial (n=139) showed the fibrin sealant EVICEL® to be effective as an adjunct to dural sutures. Intra-operative watertight closure was observed in 82/89 (92.1%) in the EVICEL group versus 19/50 (38.0%) in the control group ($p<0.001$).[8]

Avoidance of Post-Operative Drains

Post-operative drains are intended to prevent the build-up of fluid, or seroma after some types of surgery by filling “dead space”. The main concerns with seroma is that they can become infected or leak fluid and, if they remain, over time become swollen, hard and uncomfortable. Additional surgery to remove the seroma or a fine needle aspiration are both associated with increased resource use such as nursing time, hospital stay and analgesic or antibiotic use. There is contradictory evidence from two small randomised controlled trials (RCTs [n=100 and n=75]) about the use of FS as an alternative to post-operative drains during thyroid surgery. In one trial, patient outcomes were best in the FS

group; pain was significantly reduced, as was the length of time spent in hospital.[9] However, no statistically different effect on any outcome was observed in a second trial.[10] The findings from individual RCTs also suggest that post-operative pain can be reduced when FS are used in skin graft surgery.

FS are known to be ineffective in some sites; their use did not reduce leakage from oesophago-gastric anastomoses post-operatively and consequently are not recommended for surgical use at the oesophago-gastric junction.[11]

Concerns about Safety

The Food and Drug Administration (FDA) in the United States of America (USA) has issued warnings about life-threatening air or gas emboli developing after the use of fibrin sealant aerosol sprays during surgery. Users of the products have been advised about the dangers of using sprays too close to exposed tissue surfaces and at higher pressures than those recommended by the manufacturers.[12] However, despite concerns about safety, few data from RCTs exist about harms.[13] A multi-centre RCT conducted in three Italian hospitals compared the rate of adverse events in a group of patients receiving FS as an adjuvant for air-leak control in patients undergoing lung resection. Air leakage and bronco pleural fistulas in the lungs are both common complications after these procedures. With a follow-up period of 30–40 days the investigators found the rate of adverse events was not statistically significantly different between patients who received FS and those who did not.[14]

A review conducted in 2010, on the risks and complications of spinal sealants, included the two fibrin glues EVICEL and Tisseel®. It concluded that Tisseel had been used in clinical studies without adverse events. However, the review found a lack of large clinical studies on the safety of EVICEL for neurosurgery.[15] A more recent randomised controlled trial evaluating the safety of EVICEL found similar incidence of cerebrospinal leakage to 30 days post-surgery and adverse events in the EVICEL and control group. No deaths or suspected unexpected serious adverse drug reactions occurred during the trial.[8]

Authors of a systematic review of controlled trials have suggested that the beneficial patient outcomes that have been observed of FS are dependent on extensive surgeon training in the use of FS.[13]

Scope of the Short Report

While there are clear indications for the use of FS to improve patient outcomes during non-emergency surgical procedures, no over-arching summary of benefit and harms exists. Furthermore systematic reviews lack a consistent methodological approach (e.g. there are differences in the inclusion/exclusion criteria) and some systematic reviews searches were conducted some time ago and need to be updated. The purpose of this short report is to provide a consistent, up-to-date overview of the best available evidence from studies reporting the benefits and harms from the use of fibrin sealant in any non-emergency surgery. Ultimately the review will identify gaps in knowledge about the clinical effectiveness of FS and allow the mapping of evidence.

Research Questions

What are the effectiveness and safety of using a fibrin sealant prior to closure in patients undergoing non-emergency surgery?

Objectives

- To map evidence of clinical effectiveness from randomised controlled trials;
- To map evidence of adverse events from observational studies;
- Synthesis of evidence of the clinical effectiveness and adverse events of fibrin sealant in patients undergoing non-emergency surgery particularly in the reduction of seroma formation and the facilitation of haemostasis.

Planned PICO criteria

The planned criteria pertaining to population, intervention, comparators, and outcomes are summarised in Table 1.

Table 1. Planned PICO criteria

PICO	Criteria
Population	People aged ≥18, undergoing non-emergency surgery at any site in secondary care
Intervention	Any fibrin sealant product including: • Fibrin glue • Fibrin spray • Fibrin sponges, bandages • Fibrin aerosol • Fibrin tissue adhesive
Comparators	Standard Care
Outcomes	Primary outcome • Incidence of seroma Secondary outcomes

	Adverse events: • Haemostasis (blood loss) • Infection rate • Pain levels • Complications arising from the use of drains *Resource use:* • Use of analgesics • Nurse or doctor time (dressings, fine needle aspirations) • Length of hospital stay • Use of drains *Health-Related Quality of Life* In addition, an important output of the review will include an overview of gaps in knowledge to inform recommendations for future primary research, including specific outcomes for different conditions.
Study designs	Randomised controlled trials and observational studies

5. Report methods for assessing the outcomes arising from the use of the interventions

Search strategy

We will develop two search strategies: 1) search strategy for RCTs; 2) search strategy for observational studies. However, information on benefits and harms will be extracted from both studies designs. The searches for RCTs will combine terms for the technology being assessed and the study design using the Cochrane Collaboration RCT filter.[16] For observational studies, the searches will combine both controlled vocabulary terms (MeSH and EMTREE) and free text terms for general adverse events from the Centre for Review and Dissemination (CRD) guidance[17] and Cochrane guidance[18] including the following: safe, safety, side effect, undesirable effect, treatment emergent, adverse effects, contraindications and complications.

Both search strategies will include terms for the technology, which will use both controlled vocabulary terms (MeSH and EMTREE) and free text terms including the following: fibrin sealant, fibrin adhesive, fibrin glue, fibrin sponges, fibrin bandages, or aerosol and commercial names. The search strategies will be refined by scanning key papers identified during the review, through discussion with the review team, clinical experts and information specialists. Examples of the search strategies are provided in Appendix 1 and 2.

Electronic sources to be searched include: MEDLINE, EMBASE, and the Cochrane Library (including the Cochrane Database of Systematic Reviews (CDSR), the Database of Abstracts of Reviews of Effects (DARE), the Health Technology Assessment (HTA) Database, and CENTRAL).

For RCTs, ongoing and unpublished studies will be searched for using: clinicaltrials.gov, controlled-trials.com and clinicaltrialsregister.eu. For observational studies, the Food and Drug Administration (FDA) (web address: http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfmaude/detail.cfm?mdrfoi__id=4277068) and Medicines and Healthcare Products Regulatory Agency (MHRA) (web address: https://www.gov.uk/search?q=fibrin+sealants) will be searched.

Relevant reviews and guidelines will be identified through searching additional resources, including Clinical Evidence, National Institute for Health and Care Excellence (NICE) website, NIHR Health Technology Assessment Programme, Database of Abstracts for Reviews of Effectiveness (DARE) The University of York.

Reference lists of included papers will be assessed and the abstracts from key conference proceedings, to be identified in consultation with clinical experts, will be screened, where possible, for additional relevant studies. No limits relating to date or language will be applied to the searches.

Contacting clinical experts

Clinical experts in the relevant therapy area will be contacted to request details of trials (published and unpublished) of which they may be aware. Experts will be allowed 15 days to provide an initial response, with any additional time allowed being dependent on whether the data analysis stage of the review has been reached.

Abstract appraisal

Titles and abstracts of studies identified by the search process will be assessed independently by two reviewers for inclusion. In cases where the reviewers are unable to reach a consensus as to whether the full text should be obtained for further appraisal, the full text will be obtained.

When potentially relevant data are available in only an abstract format, attempts will be made to contact the corresponding author to obtain the full publication. A deadline for response to the initial contact of one calendar month will be imposed. Additional time might be allowed should the author be able to supply the data requested. Information supplied after the deadline will potentially be included only in the discussion section of the report.

Inclusion and exclusion criteria

Studies irrespective of their publication status will be included.

Studies not meeting the PICO criteria outlined in the table above will be excluded. Studies will also be excluded if they are:

- trials reporting only post-crossover results: study authors will be contacted to attempt to

obtain pre-crossover results. If pre-crossover results cannot be obtained, the study will be excluded;

- animal models;
- preclinical or biological studies;
- narrative reviews, editorials, opinions;
- reports published as only meeting abstracts, where insufficient methodological details are reported to allow critical appraisal of study quality.

A tiered approach will be used for inclusion of observational studies, where initially we will only include comparative observational studies as they are likely to provide the most robust evidence. If there is a lack of comparative observational studies, non-comparative observational studies will be included**.**

Study inclusion assessment

Two reviewers will independently assess the full text of the trials identified during the abstract assessment stage for inclusion and any differences in opinion will be arbitrated by a third reviewer. Studies rejected at this or subsequent stages will be recorded in a "characteristics of excluded studies table" and reasons for exclusion recorded.[19]

Data extraction and management

Data will be extracted by one reviewer using a standardised data extraction form (provided in Appendix 3), and independently checked by another reviewer. Information extracted will include details of the study's design and methodology, the intervention and comparators, baseline characteristics of participants, and outcome measures, including clinical outcome efficacy and any adverse events. Where there is incomplete information and if time constraints allow, attempts will be made to contact authors to request for further details. Discrepancies in the data extraction will be resolved by discussion with involvement of a third reviewer if necessary.

Data from intention-to-treat (ITT) analyses will be extracted. Should a trial not report ITT data, missing data will be treated as treatment failures to allow analysis to conform to an ITT analysis. For the purpose of this review, ITT will be defined as patients being analysed in the treatment group they were allocated to at randomisation irrespective of whether they received the allocated intervention, withdrew or were lost to follow-up.

Quality assessment strategy

The quality of included of included studies will be assessed by one reviewer and independently checked by another. Any disagreements will be resolved by consensus and if necessary a third

reviewer will be consulted. The quality of systematic reviews will be assessed according to the PRISMA checklist.[19] Observational studies will be assessed using the Newcastle-Ottawa Scale.[20] Randomised controlled trials will be assessed according to the guidance published by the Centre for Reviews and Dissemination (CRD)[17] and the Cochrane Handbook for Systematic Reviews of Interventions and recorded using the Cochrane Risk of Bias Tool.[16] An outcome from an RCT will be considered appropriate for inclusion unless the trial demonstrates some feature that necessitates the exclusion of that outcome. Seven domains will be assessed for each included study:

1. Random sequence generation;
2. Allocation concealment;
3. Blinding of participants and personnel;
4. Blinding of outcomes assessment;
5. Incomplete outcome data;
6. Selective reporting;
7. 'Other bias'.

Based on these criteria, a risk of bias assessment will be carried out for each outcome extracted. The three bias assessment categories used will be: low, high and unclear risk. Unclear risk is likely to be assigned due to poor reporting of how the trial was conducted rather than a poorly conducted trial. Trials that are deemed to be at low or unclear risk of bias will be included in the main analysis and the trials rated high risk will be included in a sensitivity analysis.

Within a study, a summary assessment of low risk of bias will be given when there was a low risk of bias for all key domains, unclear risk of bias when there is an unclear risk of bias for one or more key domains, and high risk of bias when there is a high risk of bias for one or more key domains. Across studies, a summary assessment of the risk of bias for the primary outcome (across domains) will be undertaken.

Methods of analysis/synthesis

Data will be tabulated and discussed in a narrative review. Where appropriate, meta-analysis will be implemented to estimate a summary measure of effect on relevant outcomes based on ITT analyses. For dichotomous outcomes, odds ratio will be used as the summary statistic and for continuous outcomes (weighted) mean difference will be the summary statistic. Meta-analyses will be conducted only if there are clinically homogeneous studies of similar comparisons reporting the same outcome measures. Standard pair-wise meta-analysis will be conducted when more than one trial is identified for inclusion for any pair of treatments under investigation. Meta-analysis of continuous outcomes

will be carried out with the inverse variance method[16] and for dichotomous outcomes this will be carried out using a fixed effects model with the Mantel-Haenszel method.[21] Sensitivity analysis will be conducted using a random effects model with the DerSimonian & Laird method.[22] Subgroup analyses will be performed for the subgroups for example, specific surgical indications, should the evidence allow.

Heterogeneity

For pair-wise meta-analysis, heterogeneity will be explored through consideration of the study populations, methods and interventions, by visual inspection of results and, in statistical terms, by the χ^2 test for homogeneity and the I^2 statistic. Statistically significant heterogeneity will be defined as p <0.10. Levels of inconsistency will be assessed using I^2 and will be defined as follows: I^2 of: 0%–25% = low level of inconsistency; 26%–50% = moderate level of inconsistency; and >50% = high level of inconsistency.[23]

If statistically significant heterogeneity is detected in any of the analyses, hypothesis-generating subgroup analysis will be conducted, but the results from such analyses will be treated with caution. Meta-regression will be attempted if significant statistical heterogeneity is identified among trials analysed and there are 10 or more trials in the comparison.[24]

Sensitivity analysis

Sensitivity analyses will be carried out for aspects of the review that might have an impact on the results, for example, including studies where there is a high risk of bias.[16]

Publication bias

For each of the primary pair-wise meta-analyses, a funnel plot will be used to assess publication bias when at least 10 studies are included. A regression of normalised effect versus precision will also be calculated as a test for small study effects (using a p <0.10 as an indicator of a significant result).[25]

6. Expertise in the TAR team

The BMJ-TAG is one of the Centres of Excellence identified by NIHR to undertake HTA. As a group dedicated to meeting contractual obligations to the NIHR, the BMJ-TAG has a strong record of submission of high-quality reports to tight deadlines. A brief description of the experience of the individual members of the BMJ-TAG who will contribute to this project is provided.

Dr Steven J. Edwards DPhil MSc BSc (Hons), Head of Clinical & Economic Evidence

Steve has performed clinical and economic evaluations since 1999 in a range of therapeutic areas, including cardiovascular, central nervous system, gastroenterology, infection, oncology, ophthalmology, respiratory medicine, and urology. He has in-depth experience of applying evidence

synthesis methods within the context of health technology assessment. His interests are in the use of the best available evidence for decision making with an emphasis on the design and conduct of clinical trials, systematic reviews, meta-analyses, adjusted indirect comparisons and their subsequent use in economic evaluations. His postgraduate research in this area at the University of Oxford resulted in him being awarded the first doctorate of evidence based health care in 2010. Steve is a standing member of the Diagnostic Advisory Committee for NICE and a peer reviewer of research reports for the National Institute for Health Research (NIHR). In addition, Steve is an honorary senior lecturer in health economics at the London School of Hygiene & Tropical Medicine, a member of the Cochrane Pregnancy and Childbirth Group, Cochrane Statistical Methods Group, the Campbell & Cochrane Economics Methods Group, and acts as statistical advisor to the Cochrane Skin Group.

Dr Fay Crawford PhD MSc DPodM, Senior Health Technology Assessment Analyst

Fay has wide experience of all research methods used in health services research and the evaluation of health care interventions across many clinical areas including rheumatology, dermatology, dentistry, cancer, and diabetes. Fay was awarded her PhD from the University of York in 2002. She is a member of the Cochrane Individual Patient Data (IPD) Methods group, as well as the Skin and Peripheral Vascular Diseases Groups. She is a member of an NIHR advisory board and acts as a referee for several research councils including the Medical Research Council (MRC). She is an honorary fellow at the University of Edinburgh.

Dr George Osei-Assibey PhD MSc, Health Technology Assessment Analyst

George has a PhD in Medical Science and an MSc in Human Nutrition. He previously worked as a postdoctoral fellow in systematic reviews at the University of Aberdeen, and as a senior analyst in a healthcare consultancy. He has been involved and authored publications in systematic reviews and meta-analysis for the past 9 years. George has also worked in disease areas including obesity, diabetes, cancer, cardiovascular disease, dermatology.

Dr Michelle Helena van Velthoven PhD MSc BSc, Health Technology Assessment Analyst

Michelle has an MSc in Health Technology Assessment and BSc in Biomedical Sciences from Radboud University Nijmegen, the Netherlands. She obtained her PhD in global health from Imperial College London in 2014. Michelle is a member of the Cochrane Review Group on HIV/AIDS and has worked on a number of systematic reviews in the areas of HIV and eHealth. She is an honorary research fellow at Imperial College London.

Recent publications from the TAR team

Edwards SJ, Barton S, Nherera L, Trevor N, Krause T, Thurgar E. Pixantrone monotherapy for the treatment of relapsed or refractory aggressive non-Hodgkin's lymphoma: A Single Technology Appraisal. BMJ-TAG, London, 2013.

Edwards SJ, Karner C, Trevor N, Barton S, Nherera L. Mirabegron for the treatment of symptoms associated with overactive bladder. BMJ-TAG, London, 2013.

Edwards SJ, Hamilton V, Nherera L, Trevor N. Lithium or an atypical anti-psychotic in the management of treatment resistant depression: systematic review and economic evaluation. BMJ-TAG, London, 2012.

Edwards SJ, Barton S, Thurgar E, Nherera L, Hamilton V, Karner C, *et al*. Bevacizumab for the treatment of recurrent advanced ovarian cancer: A Single Technology Appraisal. BMJ-TAG, London, 2012.

Edwards SJ, Barton S, Nherera L, Trevor N, Hamilton V. Ivabradine for the treatment of chronic heart failure: a Single Technology Appraisal. BMJ-TAG, London, 2012.

Crawford F, Cezard G, Chappell F, Murray GD, Price J, Simpson C, Sheikh A, Stansby G, Young M. Predicting foot ulceration in people with diabetes: An analysis of Individual Patient Data (IPD). NIHR Journals library 2015. *In press*

Crawford F, Chappell FM, Welch K, Andras A, Brittenden J. Ankle brachial index for the diagnosis of symptomatic peripheral arterial disease. Cochrane Database of Systematic Reviews [Protocol]. 2014, Issue 8. Art. No.: CD010680. Review in press.

Chappell FM, Crawford F, Andras A, Goodacre S, McCaslin JE, Welch K, Oates C. Duplex ultrasound for the diagnosis of symptomatic deep vein thrombosis in the lower limb. Cochrane database of systematic reviews [Protocol] 2014 Issue 1;Art No CD010930.

Crawford F, Andras A,Welch K, Sheares K, Keeling D, Chappell FM.D-dimer test for excluding the diagnosis of pulmonary embolism. Cochrane Database of Systematic Reviews 2013, [Protocol] Issue 12. Art. No.: CD010864

Crawford F**,** Anandan C, Chappell FM, Murray GD, Maxwell M, Price JF, Sheikh A, Simpson CR, Stansby GP, Young MJ, et al. Protocol for a systematic review and individual patient data meta-analysis of prognostic factors for foot ulceration in people with diabetes: the international research collaboration for the prediction of diabetic foot ulcerations (PODUS). BMC Medical Research Methodology; 2013:13:22.

Taylor EM, Hayman R, Crawford F, Jeffrey, Smith J. The impact of aid on maternal and reproductive health. A systematic review. PLoS One 2013; 8(2): e56271. doi:10.1371/journal.pone.0056271.

Allen FL, Osei-Assibey G, Arnold R, Deniz B. Indirect treatment comparison (ITC) OF therapies

often considered for treatment-experienced patients with relapsing-remitting multiple sclerosis. Value in Health, 2012; 15(4): A141.

Osei-Assibey G, Dick S, Macdiarmid J, Semple S, Reilly J.J, Ellaway A, Cowie H, McNeill G. The influence of the food environment on overweight and obesity in young children: a systematic review. BMJ Open, 2012 Dec 18;2(6). doi:pii: e001538. 10.1136.

Osei-Assibey G, Boachie C. Dietary interventions for weight loss and cardiovascular risk reduction in people of African ancestry (blacks): a systematic review. Public Health Nutrition. 2012;15(1):110-5.

Osei-Assibey G, Adi Y, Kyrou I, Kumar S, Matyka K. Pharmacotherapy for overweight/obesity in ethnic minorities and White Caucasians: a systematic review and meta-analysis. Diabetes, Obesity and Metabolism. 2011 May;13(5):385-93.

Osei-Assibey G, Kyrou I, Adi Y, Kumar S, Matyka K. Dietary and lifestyle interventions for weight management in adults from minority ethnic/non-White groups: a systematic review. Obesity Reviews. 2010 Nov;11(11):769-76.

Van Velthoven MH, Tudor Car L, Gentry S, Car J. Telephone delivered interventions for preventing HIV infection in HIV-negative persons. The Cochrane database of systematic reviews 2013;5:Cd009190.

van Velthoven MH, Brusamento S, Majeed A, Car J. Scope and effectiveness of mobile phone messaging for HIV/AIDS care: a systematic review. Psychology, health & medicine 2013;18(2):182-202.

Tudor Car L, van Velthoven MH, Brusamento S, Elmoniry H, Car J, Majeed A, et al. Integrating prevention of mother-to-child HIV transmission (PMTCT) programmes with other health services for preventing HIV infection and improving HIV outcomes in developing countries. The Cochrane database of systematic reviews 2011(6):Cd008741.

Brusamento S, Ghanotakis E, Tudor Car L, van Velthoven MH, Majeed A, Car J. Male involvement for increasing the effectiveness of prevention of mother-to-child HIV transmission (PMTCT) programmes. The Cochrane database of systematic reviews 2012;10:Cd009468.

Edwards SJ, Wakefield V, Maranezouli I, Kaner C, Marceniuk G, Azuara-Blanco A. Dexamethosone intravitreal implant for diabetic macular oedema. A Single Technology Appraisal. BMJ-TAG, London 2014.

Edwards SJ, Wakefield V, Thurgar E, Kaner C, Marceniuk G. Dabigatran etexilate for the treatment

and secondary prevention of deep vein thrombosis and/or pulmonary embolism. A Single Technology Appraisal. BMJ-TAG, London 2014.

Edwards SJ, Karner C, Trevor N, Wakefield V, Salih F. Dual-chamber pacemakers for treating symptomatic bradycardia due to sick sinus syndrome without atrioventricular block: A Multiple Technology Appraisal. BMJ-TAG, London, 2014.

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7. Competing interests of authors

None.

8. Timetable/milestones

Milestone	Date to be completed
Draft protocol	16 March 2015
Final protocol	1 May 2015
Progress report	18 September 2015
Final assessment report	23 October 2015

9. References

1. Carless PA, Henry DA, Anthony DM. Fibrin sealant use for minimising peri-operative allogeneic blood transfusion. Cochrane Database of Systematic Reviews 2009(1).

2. Cheng Y, Xiong X, Peng S, Wu Hong M, Cheng N. Fibrin sealants for the prevention of postoperative pancreatic fistula following pancreatic surgery. Cochrane Database of Systematic Reviews 2012(2).

3. Kongnyuy EJ, Wiysonge CS. Interventions to reduce haemorrhage during myomectomy for fibroids. The Cochrane database of systematic reviews 2011(11):Cd005355.

4. Liu J, Cao JG, Wang L, Ma XL. Effect of fibrin sealant on blood loss following total knee arthroplasty: a systematic review and meta analysis. International Journal of Surgery 2014;12(2):95-102.

5. Levy O MU, Oran A, Tauber C, Horosowitz H. . Use of fibrin sealant tissue adhesive to reduce blood loss and the need for blood transfusion after total knee arthroplasty. Journal of Bone and Joint Surgery Am 1999;81:1580-8.

6. Handmer M. Sticking to the facts: a systematic review of fibrin glue for pilonidal disease. ANZ J Surg 2012;82(4):221-4.

7. Morales-Conde S, Barranco A, Socas M, Alarcón I, Grau M, Casado MA. Systematic review of the use of fibrin sealant in abdominal-wall repair surgery. Hernia 2011;15(4):361-9.

8. Green AL, Arnaud A, Batiller J, Eljamel S, Gauld J, Jones P, et al. A multicentre, prospective, randomized, controlled study to evaluate the use of a fibrin sealant as an adjunct to sutured dural repair. British journal of neurosurgery 2014:1-7.

9. Sozen S, Topuz O, Tukenmez M, Keceli M. The use of fibrin sealant after total thyroidectomy for benign disease obviates the need for routine drainage. Results of a randomized controlled trial. Hippokratia 2011;15(3):247-51.

10. Kim TW, Choi SY, Jang MS, Lee GG, Nam ME, Son YI, et al. Efficacy of fibrin sealant for drainage reduction in total thyroidectomy with bilateral central neck dissection. Otolaryngology--head and neck surgery : official journal of American Academy of Otolaryngology-Head and Neck Surgery 2012;147(4):654-60.

11. Hsu HK, Hsu WH, Huang MH. Prospective study of using fibrin glue to prevent leak from

esophagogastric anastomosis. Journal of the Surgical Association 1992;25:1248-52.

12. Food and Drug Administration (USA) Risk of life-threatening air or gas embolism with the use of spray devices employing pressure regulator to administer fibrin sealants (Baxter Health Care Corporation). 2009.

13. Kjaergard HK FJ. Controlled clinical trial of fibrin sealants in cardiothoracic surgery: a review. Eur J Cardiothorac Surg 1996;10:727–33.

14. Cardillo G CF, Carbone L, De Massimi AR, Lococo A, Santini PF, Janni A, Gonfiotti A,. Adverse events of fibrin sealants in thoracic surgery: the safety of a new fibrin sealant: multi centre randomised controlled clinical trial. . Eur J Cardiothoracic Surgery 2012;41(3):657-62.

15. Epstein NE. Dural repair with four spinal sealants: focused review of the manufacturers' inserts and the current literature. The Spine Journal;10(12):1065-8.

16. Higgins JPT, Green S. Cochrane Handbook for Systematic Reviews of Interventions The Cochrane Collaboration 2011;Version 5.1.0.

17. CRD. Systematic Reviews: CRD's guidance for undertaking systematic reviews in health care 2010 Available from: http://www.york.ac.uk/inst/crd/index_guidance.htm. Date accessed: 29/04/2015

18. Loke YK, Price D, Herxheimer A. Systematic reviews of adverse effects: framework for a structured approach. BMC medical research methodology 2007;7:32.

19. Moher D, Liberati A, ., Tetzlaff J, Altman DG. The PRISMA Group. Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. BMJ 2009;339.

20. Wells GA, Shea B, O'Connell D, Peterson J, Welch V, Losos M, et al. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. Available from: http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp. Date accessed: 01/05/2015

21. Mantel N, Haenszel W. Statistical aspects of the analysis of data from retrospective studies of disease. Journal of the National Cancer Institute 1959;22(4):719-48.

22. DerSimonian R, Laird N. Meta-analysis in clinical trials. Controlled clinical trials 1986;7(3):177-88.

23. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ 2003;327(74):557-60.

24. Thompson SG, Higgins JP. How should meta-regression analyses be undertaken and interpreted? Statistics in medicine 2002;21(11):1559-73.

25. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. Bmj 1997;315(7109):629-34.

Additional information that is needed by NETSCC, HTA and NICE.

Please send this as a WORD document when you submit your protocol to Htatar@soton.ac.uk.

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10. Appendices

Appendix 1: Draft RCT search MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) search strategy (from inception to 2015)

1 exp Fibrin tissue adhesive/ (3992)
2 Fibrin Foam/ (155)
3 (fibrin adj2 glu$).tw. (3415)
4 (fibrin adj2 seal$).tw. (1546)
5 (fibrin adj2 adhesi$).tw. (676)
6 fibrin spong$.tw. (38)
7 fibrin bandag$.tw. (7)
8 fibrin aerosol$.tw. (1)
9 (biological adj2 glu$).tw. (541)
10 (biological adj2 seal$).tw. (76)
11 Beriplast.tw. (87)
12 Bolheal.tw. (10)
13 Collaseal.tw. (1)
14 Tissucol.tw. (302)
15 Tisseel.tw. (281)
16 Quixil.tw. (36)
17 Biocol.tw. (6)
18 Omrixil.tw. (1)
19 Vivostat.tw. (36)
20 Hemaseel.tw. (10)
21 Crosseal.tw. (8)
22 Tachocomb.tw. (112)
23 Tachosil.tw. (137)
24 Tissel.tw. (5)
25 Transglutine.tw. (4)
26 or/1-25 (6775)
27 Randomized Controlled Trials as Topic/ (96124)
28 randomized controlled trial/ (387346)
29 Random Allocation/ (82288)
30 Double Blind Method/ (128148)
31 Single Blind Method/ (19993)
32 clinical trial/ (490948)
33 clinical trial, phase i.pt. (14761)
34 clinical trial, phase ii.pt. (23777)
35 clinical trial, phase iii.pt. (9622)
36 clinical trial, phase iv.pt. (994)
37 controlled clinical trial.pt. (88856)
38 randomized controlled trial.pt. (387346)
39 multicenter study.pt. (181269)
40 clinical trial.pt. (490948)
41 exp Clinical Trials as topic/ (285725)

42 or/27-41 (1059020)
43 (clinical adj trial$).tw. (229125)
44 ((singl$ or doubl$ or treb$ or tripl$) adj (blind$3 or mask$3)).tw. (133359)
45 PLACEBOS/ (32653)
46 placebo$.tw. (164245)
47 randomly allocated.tw. (18131)
48 (allocated adj2 random$).tw. (20780)
49 or/43-48 (440148)
50 42 or 49 (1217384)
51 case report.tw. (215419)
52 letter/ (867687)
53 historical article/ (311107)
54 or/51-53 (1382196)
55 50 not 54 (1186930)
56 26 and 55 (788)

Appendix 2: Draft observational study search MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) search strategy (from inception to 2015)

1 exp Fibrin tissue adhesive/ (3992)
2 Fibrin Foam/ (155)
3 (fibrin adj2 glu$).tw. (3415)
4 (fibrin adj2 seal$).tw. (1546)
5 (fibrin adj2 adhesi$).tw. (676)
6 fibrin spong$.tw. (38)
7 fibrin bandag$.tw. (7)
8 fibrin aerosol$.tw. (1)
9 (biological adj2 glu$).tw. (541)
10 (biological adj2 seal$).tw. (76)
11 Beriplast.tw. (87)
12 Bolheal.tw. (10)
13 Collaseal.tw. (1)
14 Tissucol.tw. (302)
15 Tisseel.tw. (281)
16 Quixil.tw. (36)
17 Biocol.tw. (6)
18 Omrixil.tw. (1)
19 Vivostat.tw. (36)
20 Hemaseel.tw. (10)
21 Crosseal.tw. (8)
22 Tachocomb.tw. (112)
23 Tachosil.tw. (137)
24 Tissel.tw. (5)
25 Transglutine.tw. (4)
26 or/1-25 (6775)
27 adverse effects.mp. (88922)
28 contraindications.mp. (15525)
29 Intraoperative Complications/ or Postoperative Complications/ (312034)
30 ae.fs. (1395438)
31 co.fs. (1642251)
32 safe.ti,ab. (235639)
33 safety.ti,ab. (304730)
34 side effect$.ti,ab. (184400)
35 treatment emergent.ti,ab.(2294)
36 undesirable effect$.ti,ab. (2173)
37 adrs.ti,ab. (2252)
38 (adverse adj2 (effect or effects or reaction or reactions or event or events or outcome or outcomes)).ti,ab. (267285)
39 or/27-38 (3599151)
40 26 and 39 (2592)

Footnote:
ae denotes the subheading ‘adverse effects’
co denotes the subheading ‘complications’[18]

Appendix 3: Pilot data extraction form

Eligibility Criteria (PICOS)	**Yes**	**No**	**Unclear**
P: Adults undergoing non-emergency surgery at any site in a hospital setting.			
I: Any fibrin sealant product. • Fibrin glue • Fibrin spray • Fibrin sponges, bandages • Fibrin aerosol • Fibrin tissue adhesive			
C: Standard Care			
O (will be adapted for observational studies): Primary outcome: • Incidence of seroma Secondary outcomes: *Adverse events*: • Haemostasis (blood loss) • Infection rate • Pain levels • Complications arising from the use of drains *Resource use:* • Use of analgesics • Nurse or doctor time (dressings, fine needle aspirations) • Length of hospital stay • Use of drains			
S: • Randomised controlled trials • Observational studies			
Notes: (e.g. need for discussion with a second reviewer or contact with authors)			

Decision: trials must meet all the eligibility criteria (PICOS) to be included		
Include	**Exclude**	**Discuss**

Context	
Study setting (authors institution (s), surgical specialism, country)	
Trial sponsor and funder	
Recruitment period (years)	

Population		
Inclusion/ exclusion criteria:		
Total number recruited	**Intervention (n=)**	**Control (n=)**
Age (range)		
Sex (M/F)		
Number randomised (RCT) or number in group (observational studies)		
Number analysed		
Length of follow up		
Reasons for withdrawals		

Intervention	
Indication for fibrin sealant (e.g. surgical site where the procedure normally involves post-operative drainage)	
Type of fibrin sealant preparation (aerosol spray, bandage, sponge, dose, etc):	
Manufacturer:	
Active ingredients:	
Surgical site:	

Comparison		
Describe standard care (including other haemostatic products or techniques):		
Outcomes		
List all outcomes (including units of analysis), e.g: • Adverse events (infection rate, development of seroma, haemorrhage) • Use of analgesics • Nurse time • Length of hospital stay • Blood transfusion		
	Numerator/denominator or proportions (%) and standard deviations.	
Variable	Fibrin sealant group	Standard care group

Add additional rows or columns as required.

Quality assessment of RCTs (risk of bias)

Outcome	Risk of bias	Low risk	Unclear risk	High risk	Comments
Incidence of seroma	1) Random sequence generation				
	2) Allocation concealment				
	3) Blinding (participants & personnel)				
	4) Blinding of outcomes assessment				
	5) Incomplete outcome data				
	6) Selective reporting				
	7) 'Other Bias'				
Pain levels	1) Random sequence generation				
	2) Allocation concealment				
	3) Blinding (participants & personnel)				
	4) Blinding of outcomes assessment				
	5) Incomplete outcome data				
	6) Selective reporting				
	7) 'Other Bias'				
Infection rate	1) Random sequence generation				
	2) Allocation concealment				
	3) Blinding (participants & personnel)				
	4) Blinding of outcomes assessment				
	5) Incomplete outcome data				
	6) Selective reporting				
	7) 'Other Bias'				
Complications arising from the use of drains	1) Random sequence generation				
	2) Allocation concealment				
	3) Blinding (participants & personnel)				
	4) Blinding of outcomes assessment				
	5) Incomplete outcome data				

	6) Selective reporting				
	7) ‘Other Bias’				
Overall rating of bias					

Add additional rows or columns as required.

Quality assessment of observational studies (cohort)

NEWCASTLE - OTTAWA QUALITY ASSESSMENT SCALE COHORT STUDIES

Note: A study can be awarded a maximum of one star for each numbered item within the Selection and Outcome categories. A maximum of two stars can be given for Comparability.

Selection

1) Representativeness of the exposed cohort

a) truly representative of the average _____ (describe) in the community ✵

b) somewhat representative of the average _____ in the community ✵

c) selected group of users e.g. nurses, volunteers

d) no description of the derivation of the cohort

2) Selection of the non exposed cohort

a) drawn from the same community as the exposed cohort ✵

b) drawn from a different source

c) no description of the derivation of the non exposed cohort

3) Ascertainment of exposure

a) secure record (e.g. surgical records) ✵

b) structured interview ✵

c) written self report

d) no description

4) Demonstration that outcome of interest was not present at start of study

a) yes ✵

b) no

Comparability

1) Comparability of cohorts on the basis of the design or analysis

a) study controls for _____ (select the most important factor) ✵

b) study controls for any additional factor ✵ (This criteria could be modified to indicate specific control for a second important factor.)

Outcome

1) Assessment of outcome

a) independent blind assessment ✵

b) record linkage ✵

c) self report

d) no description

2) Was follow-up long enough for outcomes to occur

a) yes (select an adequate follow up period for outcome of interest) ✵

b) no

3) Adequacy of follow up of cohorts

a) complete follow up - all subjects accounted for ✵

b) subjects lost to follow up unlikely to introduce bias - small number lost - > ____ % (select an adequate %) follow up, or description provided of those lost) ✵

c) follow up rate < ____% (select an adequate %) and no description of those lost

d) no statement