MEDICAL DEVICE MATERIAL PERFORMANCE STUDY

Polycaprolactone (PCL) Safety Profile

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Executive Summary

Key Points

1. Searches identified 1322 citations; 40 articles were selected for inclusion.
2. For mesh, moderate-quality evidence from 13 studies indicated chronic pain, acute pain, hernia recurrence, foreign body sensation, seroma, and hematoma as local responses. These responses were also reported after use of other meshes (polypropylene, polyester) making the association with polycaprolactone (PCL) unclear.
3. For sutures, low-quality evidence from 3 studies indicated varying local responses including pain, granuloma, and hematoma.
4. For Nasopore sinus packing, moderate-quality evidence from 9 studies indicated acute pain, pressure and obstruction/blockage as local responses. These outcomes also occurred with non-PCL packing so the association with PCL is unclear. Low-quality evidence from 2 studies indicated that edema only occurred with PCL (versus no packing).
5. For Suprathel wound dressing, very low-quality of evidence from 2 studies indicated varying local responses including inferior Cutometer® parameters (maximal extension, retraction, pliability) with Suprathel dressing versus Biobrane dressing at 8 months.
6. For Artelon CMC spacer (an orthopedic implant), very low-quality of evidence from 3 studies indicated pain, swelling, and synovitis as local responses.
7. For Ellansé/Ellansé-M dermal filler, low-quality evidence from 3 studies indicated edema and ecchymosis as local responses. Authors of 1 study (n=780) noted that prolonged facial edema was associated with higher-volume injection of Ellansé (8.36 mL per treatment).
8. For Actifit meniscus scaffold, very low-quality evidence from 3 studies indicated local responses such as extrusion, dislocation, and synovitis.
9. For drug-eluting stents, low-quality evidence from 4 studies indicated restenosis and target lesion failure as local responses, however these outcomes occurred similarly versus non-PCL stents so the association with PCL is unclear.
10. Local responses for PCL as a material, bone filler, fixation, and nerve capping were rated very low-quality due to no evidence for these categories.
11. No evidence for systemic responses was reported.
12. The most common complication reported within surveillance data for PCL was device failure and malfunction (approximately 50% of all 86 PSO reports) with 98% of those reports related to sutures. PSO reports were split fairly evenly between sutures (56%) and meshes (43%) with a single report related to a fixation device. The most severe events were related to meshes with one leading to a patient's death after suffering a hematoma/hemorrhage during or following a surgical procedure.
13. Healthcare Technology Alerts returned 24 manufacturer issued alerts. Six alerts were related to mesh products some of which reported a high recurrence rate of post-operative hernia repairs. The remaining alerts were related to sutures many not related to biocompatibility of PCL but one alert described premature degradation of the suture. A single alert was related to bone filler, and it was described as compromised product sterility.

14. Evidence gaps:

    a. Long-term human randomized controlled trial (RCTs) for all PCL device categories. Of the 11 device categories, only 2 categories included more than 2 RCTs. In addition, follow-up for some categories (e.g., packing, sutures) was limited to ≤6 months.
    b. Additional research on systemic responses, including related patient or material factors, for all PCL device categories. Systemic responses were only investigated in 1 study which did not report responses since they weren't distinct to 1 of 2 meshes applied.
    c. Evidence for most device categories was limited to ≤2 devices of interest, with no evidence for over 70 devices of interest.
    d. Additional limitations included limited comparators (e.g., PCL meshes were mostly compared with PP meshes), limited study populations (e.g., facial dermal fillers only examined in females of Asian descent), lack of reporting study characteristics (e.g., administered dose), and lack of information on various indications (e.g., studies on mesh mostly focused on hernia repair).

Overview - Polycaprolactone

FDA engaged ECRI to perform a comprehensive literature search and systematic review to identify the current state of knowledge with regard to medical device material biocompatibility. Additionally, data derived from ECRI's Patient Safety Organization (PSO), accident investigations, Problem Reporting Network (PRN), and healthcare technology alerts were analyzed. This report focuses on answering five key questions provided by FDA and summarized below, regarding a host's local and systemic response to Polycaprolactone. If data did not exist to sufficiently address these questions, a gap was noted in this report. These gaps could represent areas of further research.

1. What is the typical/expected local host response to these materials?

Local responses/device events varied somewhat across different device categories between human studies (see specific responses/events under 1a. below).

a. Can that response vary by location or type of tissue the device is implanted in or near?

i. Ten studies examined mesh for hernia repair, while 1 study each examined mesh for abdominal aortic aneurysm repair, breast surgery, and sling surgery. Commonly reported local responses included acute and chronic pain, hernia recurrence, foreign body sensation, seroma formation, and hematoma. These responses however were also reported after use of other meshes (PP, polyester) making the association with PCL unclear. Several responses only occurred after hernia repair: acute pain (highest rate 50% at 1 month), chronic pain (rate range, 2.9% to 33.9%), and foreign body sensation (rates 47.8% at 6 months, 13% at 2 years). Seroma formation occurred with hernia repair (highest rate 21% at 21 days), abdominal wall closure, and breast surgery (rate 8.3% at 2 weeks). Hematoma occurred after hernia repair (highest rate of 16.2% at 21 days) and abdominal wall closure (2 patients). Partial dehiscence was rarely reported, and only occurred after abdominal wall closure.
ii. Local responses varied across 3 studies examining use of PCL sutures after cesarean delivery, vaginal cuff closure, and endoscopic carpal tunnel release (ECTR). Hematoma, wound separation, and seroma formation only occurred after cesarean delivery. Granuloma only occurred after vaginal cuff closure, while pain only occurred after ECTR.
iii. Nine studies examined PCL packing with Nasopore after endoscopic sinus surgery. Pain, pressure, and obstruction/blockage were the most commonly reported local responses, but these outcomes did occur with non-PCL packing. Headache and migration were rarely reported. Edema was only reported with PCL (vs. no packing) in 2 studies. Rates from 1 to 6 weeks ranged from 16% to 59%.
iv. Inflammation and skin tears were noticed on an individual's thigh after detachment of a Suprathel dressing. Only 2 human studies were included in this category.
v. Three human studies examining local responses to a PCL spacer (Artelon CMC) for basal thumb joint arthritis and carpometacarpal arthritis reported pain, swelling, and synovitis.
vi. Facial dermal filler injections with Ellanse/Ellanse-M resulted in blood accumulation (e.g., ecchymosis, hematoma), fluid accumulation (e.g., malar edema), and an inflammatory response that included

numerous macrophages and foreign body giant cells (FBGCs). Authors noted that prolonged edema was associated with higher-volume injection of Ellanse (8.36 mL per treatment).

vii. Response to Actifit meniscus scaffold included an increase of coronal meniscal extrusion and scaffold failure noted as possibly or definitely related with Actifit. This response was reported in 5 patients in a single arm study so the association with the material is unclear.

viii. Restenosis and target lesion failure were reported after drug-eluting stent (DES) placement.

b. Over what time course does this local host response appear?

i. Severe acute pain was reported at 1 month, while chronic pain was reported until 5 years postoperative with mesh. Hernia recurrences were detected at 2 to 3 months, 9 months, and 12 months with mesh. Foreign body sensation was reported from 3 months to 3 years with mesh. Seroma formation with mesh occurred 1 and 2 weeks after mastectomy, and up to 34 months after hernia repair. Seroma was also detected 30-day post cesarean with suture. Hematoma occurred at 7 days and up to 12 months postoperative with mesh, within 14 days of dermal filler injection, and 30-days post-cesarean with sutures. Partial dehiscence was detected at 30 days with mesh, while wound separation ≥1 cm was measured at 30 days with sutures. Granulation was reported up to 4 weeks from nasal packing, and detected 6 months after PCL suturing. Inflammation was reported at 10 days and 1 month with sutures, day 24 with Suprathel wound dressing, and up to 30 months with an orthopedic implant. The inflammatory response from dermal filler (including macrophages, FBGCs, eosinophils) was detected at 2 weeks, 1 year, and 4 years. Foreign body reaction including FBGCs was reported up to 5 years from an orthopedic implant. Crusting and obstruction/blockage and crusting from nasal packing was reported up to 4 weeks and up to 12 weeks, respectively. Edema was detected from 1 week to 6 weeks from nasal packing and within 14 days of dermal filler injection. Migration occurred perioperatively with nasal packing. Skin tears occurred on postoperative day 28 with Suprathel wound dressing. Instability after orthopedic implant was detected as early as 2 weeks. Swelling occurred for 1 to 2 days after dermal filler injection and up to 26 months after orthopedic implant. Synovitis occurred up to 26 months after orthopedic implant. Malar edema (later than 2 weeks to 3 years), discoloration (10 months and 11 months), and palpable lumps (within 14 days) all occurred post dermal filler injection. An increase of coronal meniscal extrusion was noted within 40 months of followup after Actifit scaffold implantation. Formation of irregular margins and reduction in size of Actifit scaffold was noted at 24 months, and after 60 months. Lastly, restenosis (in-stent and in-segment) was reported at 9-month followup with DES.

2. Does the material elicit a persistent or exaggerated response that may lead to systemic signs or symptoms – beyond known direct toxicity problems?

a. What evidence exists to suggest or support this?

1 of 40 included studies examining mastectomy/breast reconstruction with mesh investigated systemic responses. Authors only sought to report responses distinct to one mesh, and ultimately found none distinct to a PCL mesh or a mesh comprised of non-crosslinked bovine pericardium applied to opposing breasts.

b. What are the likely systemic manifestations?

No studies reported systemic manifestations from PCL devices.

c. What is the observed timeline(s) for the systemic manifestations?

Not applicable.

d. Have particular cellular/molecular mechanisms been identified for such manifestations?

Not applicable.

3. Are there any patient-related factors that may predict, increase, or decrease the likelihood and/or severity of an exaggerated, sustained immunological/systemic response?

No included studies investigated whether there are patient-related factors that may affect sustained immunological/systemic responses.

4. **Are there any material-related factors that may predict, increase, or decrease the likelihood and/or severity of an exaggerated, sustained immunological/systemic response?**

   No included studies investigated whether there are material-related factors that may affect a sustained immunological/systemic response.

5. **What critical information gaps exist and what research is needed to better understand this issue?**

   All gaps listed here could benefit from future research.
   a. Long-term human RCTs for local responses to PCL as a material and for all device categories to better ascertain associations with these responses to PCL.
   b. Additional research on systemic responses, including those on patient or material factors, for all PCL device categories.

Project Overview

FDA engaged ECRI to perform a comprehensive literature search and systematic review to identify the current state of knowledge with regard to medical device material biocompatibility. Specific materials or topics were selected by FDA based on current priority. For 2021, the following 18 topics have been chosen.

1. Magnesium (Mg)
2. Complications associated with Polypropylene Mesh in Pre-, Peri-, and Post-Menopausal Women
3. Polytetrafluoroethylene (PTFE)
4. Acrylics 1: PMMA
5. Acrylics 2: pHEMA
6. Acrylics 3: Cyanoacrylates (PET)
7. Correlations between complications with polypropylene mesh and surgical procedure/anatomical location and chemical/mechanical device properties
8. Dimethacrylates, Trimethacrylates (EDMA, EGDMA, TEGDMA, PEGDMA), and glycerol methacrylate (bis-GMA)
9. Polyethylene glycol (PEG)
10. Other Fluoropolymers (PFPE, PVDF, PVDF-HFP, PCTFE)
11. Silver
12. Small Molecule Per- and polyfluoroalkyl substances (SM-PFAS)
13. Hyaluronic Acid (HA) - Muscle/Skeletal Applications
14. Hyaluronic Acid (HA) - Dermal, Facial, and Eye Applications
15. Hyaluronic Acid (HA) – Adhesion Barriers
16. Polycaprolactone (PCL)
17. Zirconia
18. Nitinol

The systematic review was guided by key questions mutually agreed upon by FDA and ECRI. Data were extracted from literature articles and ECRI surveillance databases accordingly.

Key Questions

1. What is the typical/expected local host response to Polycaprolactone?
   a. *Can that response vary by location or type of tissue the device is implanted in or near?*
   b. *Over what time course does this local host response appear?*
2. Does the material elicit a persistent or exaggerated response that may lead to systemic signs or symptoms – beyond known direct toxicity problems?
   a. *What evidence exists to suggest or support this?*
   b. *What are the likely systemic manifestations?*
   c. *What is the observed timeline(s) for the systemic manifestations?*
   d. *Have particular cellular/molecular mechanisms been identified for such manifestations?*

3. Are there any patient-related factors that may predict, increase, or decrease the likelihood and/or severity of an exaggerated, sustained immunological/systemic response?

4. Are there any material-related factors that may predict, increase, or decrease the likelihood and/or severity of an exaggerated, sustained immunological/systemic response?

5. What critical information gaps exist and what research is needed to better understand this issue?

If data did not exist to sufficiently address these questions, a gap was noted in this report. These gaps could represent areas of further research.

Safety Profiles were written for the materials listed above to include the summary of key findings from the systematic review and surveillance search and are included in this report.

Literature Search and Systematic Review Framework

The ECRI-Penn Evidence-based Practice Center (EPC) conducts research reviews for the Agency for Healthcare Research and Quality (AHRQ) Effective Health Care (EHC) Program. ECRI's scientific staff within our Center for Clinical Excellence has authored hundreds of systematic reviews and health technology assessments on 3,500+ technologies/interventions for ECRI's public- and private-sector clients. In addition to this work, ECRI staff have coauthored several methods papers on evidence synthesis published on the AHRQ Effective Health Care website and in peer-reviewed journals.

For this project, the clinical and engineering literature was searched for evidence related to biocompatibility of each material. Searches of PubMed/Medline and Embase were conducted using the Embase.com platform. Scopus was used initially to search nonclinical literature; however, it was determined that the retrieved citations did not meet inclusion criteria and that database was subsequently dropped from the search protocol. Search limits included publication dates between 2011 and 2021 and English as the publication language. ECRI and FDA agreed on appropriate host and material response search concepts as follows:

- **Material Response**
  - Strength
  - Embrittlement
  - Degradation
  - Migration
  - Delamination
  - Leaching

- **Host Response**
  - Local
    - Inflammation
    - Sensitization
    - Irritation
    - Scarring/fibrosis
      - *Keloid formation*
      - *Contracture*
    - Ingrowth
    - Erosion
  - Systemic
    - Cancer
    - Inflammation
    - Immune Response
    - Fatigue
    - Memory Loss
    - Rash
    - Joint Pain
    - Brain Fog

Search strategies were developed for each concept and combined using Boolean logic. Several search approaches were used for comprehensiveness. Strategies were developed for devices of interest as indicated by FDA as well as the material-related strategies. Each of these sets were combined with the material and host response strategies. Detailed search strategies and contextual information are presented in Appendix B. Resulting literature was screened by title review, then abstract review, and finally full article review. Data were extracted from the articles meeting our inclusion criteria to address the key questions for each material.

ECRI Surveillance Search Strategy

There are four key ECRI sources for medical device hazards and patient incidents. These databases were searched by key terms and device models. Relevant data were extracted to address the key questions agreed upon by FDA and ECRI. Patient demographics were extracted when available. All data presented were redacted and contain no protected health information (PHI).

ECRI surveillance data comprise ECRI Patient Safety Organization (PSO) event reports, accident investigations, problem reporting network (PRN) reports, and alerts. The PSO, investigations, and PRN reports included in this report include mostly acute patient events. We rarely find chronic conditions or patient follow-up reports, which are more prevalent in the clinical literature. Complications are reported directly by clinical staff, thus reports vary greatly in the level of detail provided.

ECRI Patient Safety Organization (PSO)

ECRI is designated a Patient Safety Organization by the U.S. Department of Health and Human Services and has collected more than 3.5 million serious patient safety events and near-miss reports from over 1,800 healthcare provider organizations around the country. Approximately 4% of these reports pertain to medical devices. Most of these reports are acute (single event) reports and do not include patient follow-up. These data were filtered by complication, and relevant reports were included in the analysis. "Harm Score" refers to the National Coordinating Council Medication Error Reporting and Prevention (NCC MERP) taxonomy of harm, ranging from A to I with increasing severity (see Figure 1). The entire PSO database was included in the search, with reports ranging from year 2004 through August 2021, unless otherwise noted.

Figure 1. NCC MERP "harm score," which is now regularly used by patient safety organizations.

Category A (No Error)
Circumstances or events that have the capacity to cause error.

Category B (Error, no harm)
An error occurred, but the error did not reach the patient (an "error of omission" does reach the patient).

Category C (Error, no harm)
An error occurred that reached the patient but did not cause patient harm.

Category D (Error, no harm)
An error occurred that reached the patient and required monitoring to confirm that it resulted in no harm to the patient and/or required intervention to preclude harm.

Category E (Error, harm)
An error occurred that may have contributed to or resulted in temporary harm to the patient and required intervention.

Category F (Error, harm)
An error occurred that may have contributed to or resulted in temporary harm to the patient and required initial or prolonged hospitalization.

Category G (Error, harm)
An error occurred that may have contributed to or resulted in permanent patient harm.

Category H (Error, harm)
An error occurred that required intervention necessary to sustain life.

Category I (Error, death)
An error occurred that may have contributed to or resulted in patient death.

Definitions
Harm: Impairment of the physical, emotional, or psychological function or structure of the body and/or pain resulting therefrom.
Monitoring: To observe or record relevant physiological or psychological signs.
Intervention: may include change in therapy or active medical/ surgical treatment.
Intervention necessary to sustain life: includes cardiovascular and respiratory support (eg CPR, defibrillation, intubation).

Accident Investigation

ECRI has performed thousands of independent medical-device accident investigations over more than 50 years, including on-site and in-laboratory investigations, technical consultation, device testing and failure analysis, accident simulation, sentinel event and root-cause analyses, policy and procedure development, and expert consultation in the event of litigation. Our investigation files were searched by keywords, and the search was limited to the past 10 years unless we found landmark investigations that are particularly relevant to biocompatibility.

Problem Reporting Network (PRN)

For more than 50 years, ECRI's Problem Reporting Network (PRN) has gathered information on postmarket problems and hazards and has been offered as a free service for the healthcare community to submit reports of medical device problems or concerns. Each investigation includes a search and analysis of the FDA MAUDE database for device-specific reports. Based on our search findings, we may extend our analysis to all devices within that device's FDA-assigned product code. The PRN database was searched by keywords, and the search was limited to the past 10 years.

Healthcare Technology Alerts

We regularly analyze investigation and PRN data to identify trends in use or design problems. When we determine that a device hazard may exist, we inform the manufacturers and encourage them to correct the problem. ECRI publishes the resulting safety information about the problem and our recommendations to remediate the problem in a recall-tracking management service for our members. The Alerts database contains recalls, ECRI exclusive hazard reports, and other safety notices related to Medical Devices, Pharmaceuticals, Blood Products, and Food Products. This database was searched by keywords and specific make and model, and the search was limited to the past 10 years.

Safety Profile - Polycaprolactone (PCL)

Full Name: Polycaprolactone
CAS Registry Number: 24980-41-4

Safety Brief - Systematic Review Results

The systematic review included clinical and engineering literature on biocompatibility (i.e., host response and material response) of Polycaprolactone (PCL) used in medical devices. In addition to fundamental material biocompatibility, we focused on specific devices known to be made of Polycaprolactone. The devices in Table 1 were recommended by FDA CDRH to guide ECRI in searching this literature and ECRI's surveillance data.

Table 1: Medical Devices Containing PCL provided by FDA to Guide ECRI Searches

Regulatory Description	Product Code	Class
Dressing, Wound, Drug	FRO	Unclassified
Mesh, Surgical, Polymeric	FTL	2
Mesh, Surgical	FTM	2
Suture, Absorbable, Synthetic, Polyglycolic Acid	GAM	2
Suture, Absorbable, Synthetic	GAN	2
Suture, Nonabsorbable Synthetic, Polyamide	GAR	2
Suture, Nonabsorbable, Synthetic, Polyethylene	GAT	2
Methyl Methacrylate for Cranioplasty	GXP	2
Cover, Burr Hole	GXR	2
Plate, Fixation, Bone	HRS	2
Screw, Fixation, Bone	HWC	2
Plate, Bone	JEY	2
Cuff, Nerve	JXI	2
Prosthesis, Wrist, Carpal Trapezium	KYI	2
Splint, Intranasal Septal	LYA	1
Fastener, Fixation, Biodegradable, Soft Tissue	MAI	2
Filler, Bone Void, Calcium Compound	MQV	2
Suture, Surgical, Absorbable, Polydioxanone	NEW	2
Polymer, Ear, Nose and Throat, Synthetic, Absorbable	NHB	2
Mesh, Surgical, Synthetic, Urogynecologic, for Apical Vaginal and Uterine Prolapse, Transabdominally Place	OTO	2
Mesh, Surgical, Synthetic, Urogynecologic, for Pelvic Organ Prolapse, Transvaginally Place	OTP	3

The Safety Brief summarizes the findings of the literature search on toxicity/biocompatibility of PCL. Inclusion/exclusion criteria and quality of evidence criteria appear in Appendix A in the Appendices document. Quality of evidence ratings reflected a combination of the quality of comparative data (study designs), quantity of evidence (number of relevant studies), consistency of evidence, magnitude of effect, directness of evidence, and evidence for a dose response or response over time. The search strategy appears in Appendix B, and a flow diagram documenting inclusion/exclusion of studies appears in Appendix C.

We included 39 studies reported in 40 publications. Summary evidence tables with individual study data appear in Appendix D, and a reference list of studies cited in the Safety Brief appears in Appendix E.

A summary of our primary findings is shown in Table 2. We then turn to a detailed discussion of research on PCL as a material as well as research on the various device categories.

In the discussion section, please note that a statement of "no difference" or "no significant difference" between devices/materials does not imply equivalence between devices/materials, as studies with low numbers of patients or events often lack sufficient statistical power to detect a difference between comparators. In addition, when we cite odds ratio(s), an odds ratio >1 means that the rate was higher in the PCL group than in the non-PCL group.

Table 2: Summary of Primary Findings from our Systematic Review

Application	Local Host Responses/Device Events	Quality of Evidence (local responses)	Systemic Responses	Quality of Evidence (systemic responses)
Polycaprolactone as a material	No studies	Very low (no evidence)	No studies	Very low (no evidence)
Mesh (13 human studies)	Bleeding (perioperative and postoperative), de novo urgency, discomfort sensation, foreign body sensation, hematoma, hernia recurrence, incontinence, ischemic orchitis, neuralgia, pain (acute, chronic, abdominal wall, sexual-related, testicular), partial dehiscence, seroma formation, suture granuloma, urinary retention, vaginal erosion/extrusion	Moderate for pain (acute and chronic), hernia recurrence, foreign body sensation, seroma, and hematoma. Low for all other local responses/device events	1 study investigated but did not report systemic responses	Very low (no evidence)
Sutures (3 human studies)	Acute pain, granuloma, hematoma, inflammation, seroma, wound separation	Low	No studies investigated	Very low
Bone filler	No studies	Very low (no evidence)	No studies	Very low (no evidence)
Fixation	No studies	Very low (no evidence)	No studies	Very low (no evidence)
Packing – ear and nasal (9 human studies)	Acute pain, bleeding upon removal, crusting, edema, granulation, headache, migration, obstruction/blockage, pressure, stenosis	Moderate for acute pain, pressure, and obstruction/blockage. Low for other local responses/device events	No studies investigated	Very low
Dressing (2 human studies)	Detachment, inferior Cutometer® parameters (maximal extension, elasticity, retraction, pliability), inflammation, skin tears	Very low	No studies investigated	Very low
Orthopedic implant (3 human studies)	Chronic pain, foreign body reaction, instability, swelling, synovitis/inflammation	Very low	No studies investigated	Very low

Application	Local Host Responses/Device Events	Quality of Evidence (local responses)	Systemic Responses	Quality of Evidence (systemic responses)
Nerve capping	No studies	Very low (no evidence)	No studies	Very low (no evidence)
Dermal filler (3 human studies)	Blood accumulation (bruising, ecchymosis, hematoma), discoloration at injection site, fluid accumulation (edema, malar edema), inflammatory response, palpable lumps, swelling	Low for edema and ecchymosis. Very low for other local responses/device events	No studies investigating	Very low
Meniscus scaffold (3 human studies)	Chronic pain; extrusion; dislocation, non-integration, tearing of scaffold; irregular margins and scaffold size reduction; failure/reoperation due to pain; stiffness; synovitis	Very low	No studies investigating	Very low
Drug-eluting stent (4 human studies)	Restenosis, TLF (cardiac death, TV-related MI, or ischemic-driven TLR/clinically indicated TLR), TLR, TV-related MI	Low	No studies investigating	Very low

MI: myocardial infarction; TLF: target lesion failure; TLR: target lesion revascularization; TV: target vessel

Mesh

13 human studies (2 SRs[1,2] and 11 RCTs.[3-13] For further information see Table 1 in Appendix D.

Local Responses/Device Events (human studies)

12 studies examined Ultrapro, a lightweight mesh (LWM) composed of approximately equal parts of absorbable poliglecaprone (PGC) and nonabsorbable polypropylene (PP). The following comparisons were made:

- Ultrapro mesh versus heavyweight mesh (HWM)
  - Parietex mesh composed of polyester[4]
  - Prolene mesh composed of non-absorbable PP[1,2,5,9,11,12]
- Ultrapro mesh versus Optilene mesh composed of non-absorbable PP[7,8,13]
- Ultrapro mesh versus conventional laparotomy closure with sutures (no mesh)[6]
- Ultrapro mesh versus 2 other synthetic meshes (Prolene, Vypro)[10]

1 study examined a synthetic PCL mesh (TIGR Matrix Surgical) versus a biological mesh comprised of non-crosslinked bovine pericardium (Veritas Collagen Matrix).[3]

Follow-up for 11 (85%) studies was 1 year to 5 years. Over 2900 patients received a PCL mesh; most studies enrolling middle-aged males undergoing hernia repair[1,2,4,5,7-9,11-13] or elective abdominal aortic aneurysm repair.[6] 2 studies enrolled females only[3,10] aged 25 years to 65 years undergoing bilateral mastectomy and immediate breast reconstruction,[3] and mean 50 years undergoing sling surgery for stress incontinence.[10] Dose was not reported in any study; features such as weight, thickness and pore size were rarely reported.[1,4,5,9]

More commonly reported local responses were chronic pain, hernia recurrence, foreign body sensation, seroma formation, acute pain and hematoma.

Chronic pain: Of the 8 studies reporting this outcome, 3 RCTs comparing Ultrapro mesh with a PP mesh (Optilene, Prolene) reported higher[8] or significantly higher[5,7] pain rates with Ultrapro. The 1st RCT (n=134) reported more mild to severe chronic pain with Ultrapro at 6 months.[8] The 2nd RCT reported significantly more patients with clinically relevant postoperative pain with Ultrapro at 1 year (n=894; 2.9% vs. 0.7%) and 2 years (n=867; 3% vs. 0.9%).[5] A multivariate analysis in this study indicated that Ultrapro was associated with significantly more relevant pain at 1 year (OR 3.96, 95% CI: 1.10 to 14.23; p=0.04).[5] The 3rd RCT (n=128) reported significantly more chronic pain with Ultrapro at 3 years (33.9% vs. 15.9%; p=0.02).[7] Authors of this study cautioned that considering the fact that the absorbable component of Ultrapro, polyglecaprone, is fully absorbed during 84–140 days, it is therefore unlikely that the different composition of the meshes is the only reason why more patients reported pain with Ultrapro.

Of the remaining 5 studies, 4 studies (n=3309) reported no significant differences in chronic pain with Ultrapro mesh vs. PP meshes from 3 months to 5 years.[1,2,9,11] Multivariate analysis in 1 RCT (n=917) indicated that mesh type was not a predictor of pain after 3 months (OR 0.91, 0.65 to 1.28; p=0.60),[9] while a multivariate analysis from another RCT (n=356) indicated that mesh type was significantly associated with postoperative pain.[11]

Lastly, 1 RCT (n=80) reported similar pain scores with Ultrapro mesh vs. Optilene PP mesh at 6 months (0.47 PCL, 0.52 PP).[13]

Hernia recurrence: Of the 7 studies reporting this outcome, 1 RCT reported a similar recurrence rate of 0.4% between Ultrapro and Prolene at 3 months, but higher recurrence rates with Ultrapro at 1 year (n=894; 1.7% vs. 0.6%) and 2 years (n=867; 2.7% vs. 0.8%; p=0.03). Multivariate analysis indicated that Ultrapro was associated with a significantly higher recurrence rate at 2 years (odds ratio 3.30, 95% CI: 1.06 to 10.29; p=0.04).[5]

The remaining 6 studies (n=4092)(2 SRs[1,2] and 4 RCTs[4,9,11,12]) reported no significant difference in rates[1,2,4,11] or similar rates[9,12] with Ultrapro versus Prolene from 3 months[9] up to 3 years.[1] Rates ranged from 0.4% to 2.1% for Ultrapro and 0.4% to 0.9% with Prolene. 1 study reported recurrence only occurred with Ultrapro vs. a polyester mesh (2 vs. 0; p=0.15). Hernias were specifically detected at 2 to 3 months in 1 study[9] and at 9 months and 12 months postoperative in another study.[4]

Foreign body sensation: Of the 7 studies reporting this outcome, 1 SR of 2 RCTs (n=617) reported significantly lower rates with Ultrapro versus PP meshes at 1 year (14% vs. 23.6%; risk ratio (RR) 0.6, 95% CI: 0.36 to 0.98) and at 3 years (1% vs. 8.8%; RR 0.12, 95% CI: 0.02 to 0.91).[1]

Of the remaining studies, 5 RCTs (n=2158) reported higher but not significantly different occurrence with Ultrapro vs. PP meshes[5,7-9] or polyester mesh[4] from 3 months to 3 years. Results included the following:

- vs. Optilene at 6 months (47.8% vs. 31.3%)[8] and 3 years (23.1% vs. 15.9%),[7]
- vs. Prolene at 3 months (20% vs. 17.6%),[9] at 1 year (13.8% vs. 12.2%),[5] and 2 years (13.8% vs. 12.2%),[5]
- vs. Parietex in discomfort levels at rest (0.5 vs. 0), from lying to sitting (0.15 vs. 0.11), or exercise (0.1 vs. 0) at 12 months.[4]

Lastly, 1 RCT (n=309) reported similar rates (3 each arm) with Ultrapro vs. Prolene at 12 months.[12]

Seroma formation: Of the 6 studies reporting this outcome, 2 studies reported significantly lower seroma formation with a PCL mesh.[3,4] The 1st RCT (n=24) reported significantly lower seroma formation with TIGR Matrix Surgical Mesh versus Veritas Collagen Matrix Mesh (8.3% vs. 38%; p=0.01) in females undergoing breast reconstruction. Seroma occurred 1 and 2 weeks after mastectomy.[3] The 2nd RCT (n=85) reported significantly lower seroma formation with PCL mesh vs. a polyester mesh up to 34 months (2 vs. 9; p=0.02).[4]

1 SR of 2 RCTs (n=1002) reported no significant difference with Ultrapro vs. Prolene in development of postoperative seroma up to 12 months.[2]

3 RCTs reported mixed results. 1 RCT (n=114) reported seroma formation only with Ultrapro vs. conventional closure with sutures (2 vs. 0) up to 30 days.[6] 1 RCT (n=134) reported similar seroma formation (1 Ultrapro, 2 Optilene) at 1 month.[8] Lastly, 1 RCT (n=80) reported higher rates with Ultrapro vs. PP meshes at 21 days (21.6% vs. 17.1%), but lower rates with Ultrapro at 6 months (2.94% vs. 6.45%).[13]

Acute pain: 5 studies reporting this outcome compared Ultrapro with a PP mesh (Prolene, Optilene). 1 RCT (n=134) reported higher rates for acute pain with Ultrapro at 1 week (90% vs. 81%) and 1 month (52.3% vs. 41.8%). At 1 month, patients reported less mild pain (4.5% vs. 11.9%), but more moderate pain (40.3% vs. 23.9%) and severe pain (7.5% vs. 6%) with Ultrapro.[8]

3 studies reported no significant difference in rates[2,9] or similar rates[13] for acute pain from 1 day to 6 weeks (n=917; rates ranged from 95% to 30% with Ultrapro, and 94% to 26% with PP),[9] at 7 days (n=402),[2] and at 21 days (n=80).[13] Lastly, 1 RCT (n=356) reported less frequent pain with Ultrapro at 3 months.[11]

Hematoma: Of 5 studies reporting hematoma, 3 RCTs (n=1360) reported similar rates. 1 RCT reported hematoma in 9 patients each with Ultrapro vs. Optilene at day 7 postoperative.[8] The other 2 RCTs, examining Ultrapro vs. Prolene, reported 12% rates each arm at 3 months,[9] and 1 occurrence each arm 30 days to 12 months.[12]

Of the remaining 2 RCTs, 1 RCT (n=80) reported less minor hematoma with Ultrapro vs. Optilene (16.2% vs. 25.7%) at 21 days,[13] while 1 RCT reported that hematoma only occurred with Ultrapro vs. conventional closure with sutures (2 vs. 0) within 30 days postoperatively.[6]

Less commonly reported outcomes were discomfort sensation (2 studies); and urinary retention, sexual-related pain, testicular pain, abdominal wall pain, partial dehiscence, perioperative bleeding, postoperative bleeding, de novo urgency, incontinence, suture granuloma, urinary retention, vaginal erosion, ischemic orchitis, and neuralgia in 1 study each.

While most studies reported similar occurrence of these outcomes versus comparators, 1 RCT (n=94)[10] reported significantly lower occurrence with Ultrapro vs. 2 other synthetic meshes for the following outcomes up to 4 years:

- vaginal erosion/extrusion (2.1% Ultrapro, 4.3% with Vypro and Prolene) occurred at mean 12.3 months,
- suture granuloma (2.1% Ultrapro, 6.5% Vypro, 6.4% Prolene),
- incontinence (2.1% Ultrapro, 8.7% Vypro, 8.5% Prolene) measured at 4 years,
- de novo urgency (4.2% Ultrapro, 10.9% Vypro, 8.5% Prolene)

Lastly, 2 studies reported two local responses only occurred with Ultrapro:

- urinary retention: 3 Ultrapro vs. 0 Parietex; retention resolved by mean 10.6 days,[4]
- partial dehiscence: 1 Ultrapro vs. 0 conventional closure up to 30 days[6]

Systemic Responses

1 RCT,[3] investigating TIGR Matrix Surgical mesh vs. Veritas Collagen Matrix mesh, did not report systemic responses "that could not be related to 1 of the breasts."

Overall Quality of Evidence

The quality of evidence was rated moderate for pain (acute and chronic), hernia recurrence, foreign body sensation, seroma, and hematoma due to consistent reporting of these outcomes from higher-quality studies with large enrollment; some outcomes in agreement with other PCL devices (e.g., suture, packing, orthopedic implant, meniscus scaffold). For other outcomes reported in fewer studies, the quality of evidence is low. For systemic responses, the quality of evidence was rated very low.

Sutures

3 human studies (1 RCT,[14] and 2 nonrandomized comparative studies[15,16]. For further information see Table 2 in Appendix D.

Local Host Responses (human studies)

Studies analyzed PCL sutures (Monocryl,[14] Polysorb,[15] Caprosyn[16]) versus non-PCL closure methods including other sutures (polyglactin 910,[14] polyglyconate[15]) and an adhesive bandage.[16] 468 patients received PCL sutures for disorders such as obstetrical and gynecological (100% female) to endoscopic wrist surgery (gender not disclosed). Mean age was 31 to 48 years, and follow-up ranged from 10 days to 6 months.

Hematoma: One RCT[14] reported that 1 PCL suture patient (0.4%) displayed hematoma at the 30-day post-cesarean outpatient visit, compared with 2 patients (0.9%) in the comparative non-PCL suture group (relative risk (RR) 0.41, 95% CI: 0.04 to 4.49).

Wound separation: One RCT[14] reported that 8 (3%) PCL suture patients displayed wound separation of 1 cm or greater in length at the 30-day post-cesarean outpatient visit, compared with 8 (3.7%) patients in the comparative non-PCL suture group (RR 0.82, 95% CI: 0.31 to 2.15).

Seroma: One RCT[14] reported that 1 (0.4%) PCL suture patient displayed seroma at the 30-day post-cesarean outpatient visit, compared with 2 (0.9%) patients in the non-PCL suture group (RR 0.41, 95% CI: 0.04 to 4.49). In this RCT,[14] PCL suture was associated with a 40% reduction in the rate of wound complications when compared with the non-PCL suture.

Granuloma: One nonrandomized comparative study[15] reported that 8 (4.3%) PCL suture patients experienced granulation of the vaginal cuff after six months, compared with 6 (2%) patients in the comparative group of non-PCL barbed suture.

Inflammation: One nonrandomized comparative study[16] reported that 3 (14.3%) PCL suture patients reported inflammation at 10 days and 1 month, with no inflammation reported with adhesive bandages.

Acute pain: One nonrandomized comparative study[16] reported no significant difference in degree of pain with PCL sutures versus adhesive bandages.

Systemic Responses

We did not identify any studies investigating systemic responses to PCL as suture.

Overall Quality of Evidence

The evidence for all outcomes was inconsistent across studies, however all studies had control groups, so the quality of evidence is low. For systemic responses, the quality of evidence was rated very low (no studies investigating).

Packing – ear and nasal

9 human studies (2 SRs[17,18] and 7 RCTs[19-25]). For further information see Table 3 in Appendix D.

Local Host Responses (human studies)

In general, studies analyzed patients receiving PCL packing with Nasopore (Polyganics and Stryker) versus non-PCL nasal packing or no packing[21,25] after endoscopic sinus surgery for bilateral chronic rhinosinusitis (or similar condition). These studies tended to randomize the nasal cavity in which patients received either type of nasal packing, so they reported outcomes on both materials for each patient. A total of 1051 patients received PCL packing with a sample size of 19 to 187 patients. Studies enrolled 29% to 60% females, with an age range of 5 to 76 years (mean of approximately 42 years). Follow-up ranged from immediately postoperative to 3 months.

Acute pain: 3 RCTs[21-23] and 2 SRs[17,18] reported on VAS scores for pain during packing, in situ, and/or during removal. Most studies[17,21-23] reported no significant difference in pain between groups immediately after surgery up to 12 weeks follow-up. 1 SR[18] reported that pain in situ (5 RCTs: standardized mean difference (SMD) -0.68; 95% CI, -1.16 to -0.20; p=0.005) and pain upon removal (6 RCTs: SMD -1.62; 05% CI, -2.3 to -0.71; p=0.005) were significantly lower with PCL. Generally, pain scores during removal for PCL-treated sides were zero or low, as the material is bioresorbable and does not require removal – this generally leads to an increase in patient satisfaction overall.

Pressure: 1 SR of 4 RCTs[18] and 3 RCTs[22-24] reported VAS scores for sensation of nasal cavity pressure after packing. In two studies,[18,22] there was significantly lower pressure sensation reported in the PCL-treated groups at 10 days (follow-up NR for the SR[18]). In 2 RCTs,[23,24] there was no significant difference in pressure sensation between the treated sides on the day of surgery throughout 12 week follow-up.

Obstruction/Blockage: 1 SR of 4 RCTs[18] and 3 RCTs[22-24] reported VAS scores for obstruction/blockage after packing. In two studies,[18,24] there was no significant different in blockage between the treatment sides. In 1 RCT,[22] the PCL-treated side had significantly lower blockage at the 2nd and 10th days, but no significant difference by day 30. Conversely, 1 RCT[23] reported significantly higher blockage ratings on the PCL-treated side with 12 week follow-up.

Crusting: 3 RCTs[19,23,25] reported crust formation after nasal packing. In 1 RCT,[19] 25 patients (50%) had moderate crusting in the PCL-packed sinus cavity after 1 week, compared to 14 patients (28%) on the comparative side. After 3 weeks, 27 patients (54%) had moderate and severe crusting on the PCL side compared to 13 patients (26%) on the comparative side. By week 4, there were no significant differences between treatments with regards to crusting. In 1 RCT,[23] the mean score for crusting at 1 and 2 weeks was significantly higher on the PCL-treated side. In 1 RCT,[25] crust formation occurred in a higher number of patients in the PCL-packed side, but the degree of crusting was higher in the control (unpacked side) at 4 week follow-up. In 1 RCT,[21] PCL-treated sides did not feature crusting at any time point.

Granulation: 3 RCTs[19,21,23] reported granulation after nasal packing. In 1 RCT,[19] 36 patients (72%) had moderate granulation in the PCL-packed sinus cavity after 1 week, compared to 24 patients (36%) on the comparative side. After 3 weeks, 27

patients (54%) had no or mild granulation on the PCL side, versus 40 patients (80%) on the comparative side. After 4 weeks, 40 patients (80%) had no or mild granulation on the PCL side versus 46 patients (92%) on the comparative side.

In 1 RCT,[21] 23 patients (62%) and 6 (16%) displayed respectively mild and moderate granulation on the PCL side, leading to a significantly higher difference with the comparative side ($p<0.01$). Lastly, 1 RCT[23] reported significantly more severe granulation formation on the PCL-packed side at one month.

Stenosis: 2 RCTs[19,23] reported on frontal sinus ostium stenosis after nasal packing. 1 RCT[19] reported no stenosis in 20 patients (40%) on the PCL-packed side at 12 weeks, compared with 34 patients (68%) on the comparative side. In 1 RCT[23] there was no significant difference between treatment groups in terms of mean stenosis scores throughout 12 week follow-up.

Edema: 2 RCTs[21,25] reported edema after nasal packing. In 1 RCT,[21] there was mild edema on the PCL-treated side with 6, 22, and 6 patients (16%, 59%, and 16%) at weeks 1, 2, and 6, respectively. In 1 RCT,[25] edema was comparable between PCL-packed and control sides at 4 week follow-up.

Headache: 1 RCT[22] reported headache after nasal packing, with lower scores for the PCL-treated side throughout 30 day follow-up.

Migration: 1 RCT[24] reported on nasal packing migration, with 2 patients (6.6%) developing bleeding as a result of posterior migration of the PCL-material, requiring additional packing on the day of surgery.

Bleeding upon removal: 1 SR[18] reported on bleeding upon nasal packing removal, with the PCL-treated group having significantly better control of bleeding upon removal (6 RCTs: SMD, -0.99; 95% CI, -1.65 to -0.34; p=0.003). Note that PCL nasal packing is bioresorbable and does not typically require removal.

No adverse events: One RCT[20] had no recorded complications or adverse events related to PCL nasal packing during the follow-up period of 30 days.

Systemic Responses

We did not identify any studies investigating systemic responses to PCL as packing.

Overall Quality of Evidence

The quality of evidence for acute pain, pressure, and obstruction/blockage was rated moderate due to the consistency in reporting across higher-quality studies with overall large enrollment; reporting of pain in agreement with other devices (e.g., mesh, sutures). For other outcomes reported in fewer studies, the quality of evidence is low. For systemic responses, the quality of evidence was rated very low (no studies investigating).

Dressing

2 human studies (1 SR,[26] and 1 nonrandomized comparative study[27]). For further information see Table 4 in Appendix D.

Local Responses/Device Events (human studies)

The SR[26] included 14 studies (n = 331) of Suprathel (PolyMedics Innovations) wound dressing to treat burns. Due to the lack of information on the safety of Suprathel in this review, we pursued information on the individual studies. This SR consisted of 3 RCTs, 4 nonrandomized comparative studies, 4 single arm studies, and 3 case reports (data on 2 studies unavailable). Evidence from the RCTs indicated better attachment and adherence to wounds with Suprathel vs. Omiderm dressings, and excellent plasticity with attachment and adherence with Suprathel vs. Jelonet. Evidence from the nonrandomized comparative studies indicated no inflammatory reaction up to 3 weeks with Suprathel or Oasis porcine-derived wound dressing, and pain-free removal of Suprathel after complete healing of the wound. Additionally, one study indicated inferior Cutometer® parameters (e.g., maximal extension, elasticity, retraction, and pliability) with Suprathel vs. Biobrane at 8 months; no significant differences however were reported for viscoelastic analysis. Evidence from the single arm studies indicated good elasticity of Suprathel especially in areas of difficult contour, and complete detachment of Suprathel in 9 (43%) patients at 3 to 5 days postapplication. Authors noted the detachment may be due to lack of debridement with VersaJet hydrosurgery since no detachment was detected in this group.

The nonrandomized study[27] examined five patients, each of whom received both Suprathel and nanofibrillar cellulose wound dressings, and reported that two patients experienced some irritation in skin graft donor sites after Suprathel was removed (skin tears on postoperative day 28, inflammation approximately postoperative day 24).

Systemic Responses

We did not identify any studies investigating systemic responses to PCL as dressing.

Overall Quality of Evidence

For local responses, evidence was inconsistent across studies with 50% of individual studies being low quality, so we rated the quality of evidence as very low. The quality of evidence for systemic responses was also rated very low (no studies investigating).

Orthopedic implant

3 human studies (2 SRs[28,29] and 1 nonrandomized comparative study[30]). For further information see Table 5 in Appendix D.

Local Host Responses (human studies)

A PCL spacer (Artelon CMC) was examined in 1 SR,[28] while a PCL spacer versus traditional surgery (trapeziectomy) was examined in the other SR[29] and the nonrandomized comparative study.[30] A total of 148 patients received the spacer for basal thumb joint osteoarthritis[28,29] and carpometacarpal arthritis.[30] Sample size was 32 to 63 with studies mostly enrolling females (when reported). Follow-up ranged from 1 year to 30 months. Outcomes were generally unfavorable, with authors concluding to discontinue use of the implant due to pain and reoperation/explantation rates.

Foreign body reaction: Three single arm case series included in an SR[28] investigated foreign body type cells within soft tissue and bone upon histological analysis after explantation; two studies had evidence of foreign body reaction in up to one-third of patients within 5 year follow-up, while one study had no evidence of foreign body reaction.

Instability: In the nonrandomized comparative study,[30] problems with early joint instability after Artelon implantation led to an increase in prescribed splinting from 2-3 weeks to 5-6 weeks.

Chronic pain: A single arm study within an SR[28] reported 7 patients (24%) with persistent pain up to 26 months. 1 RCT within the other SR[29] reported no significant difference in reoperation due to pain in 6 patients (9.5%; RR=0.14, 95% CI: 0.01 to 2.36). No reoperations due to pain were required with trapeziectomy.

Swelling: A single arm study within an SR[28] reported on 3 patients (10%) with swelling up to 26 months. One RCT within an SR[29] reported swelling with Artelon in 21 patients (33%) compared to 1 patient (3%) receiving traditional trapeziectomy at 1 year follow-up.

Synovitis/Inflammation: A single arm study within an SR[28] reported on 1 patient (3%) with synovitis up to 26 months follow-up. In 1 nonrandomized comparative study,[30] 12 patients (37%) required revision surgery and salvage arthroplasty at 30 months follow-up due to recurrent arthritis symptoms or inflammatory reaction compared to 0 patients in the traditional surgery group.

Systemic Responses

We did not identify any studies investigating systemic responses to PCL as orthopedic implant.

Overall Quality of Evidence

For local responses, evidence was inconsistent across studies with most individual studies being low quality, so we rated the quality of evidence as very low. The quality of evidence for systemic responses was also rated very low (no studies investigating).

Dermal filler

3 human studies (3 single arm studies[31-33]). For further information see Table 6 in Appendix D. Studies examined Ellansé or Ellansé-M (Sinclair Pharmaceuticals, London, UK) facial dermal filler injections in mostly females of Asian descent aged 20 to 68 years.

Local Host Responses (human studies)

A 2020 retrospective single arm study reviewed complications from Ellansé treatments administered by a single clinician over a 3-year period.[31] Patient characteristics were not reported (graphics of female patients only). The study reviewed 780 patients (1111 treatments in the subcutaneous or supraperiosteal level of the facial areas, average dose 5.04 mL) who were followed for at least one year, with the following adverse events reported: 50 cases (4.5%) of edema that lasted longer than

2 weeks (prolonged edema), 30 cases (2.7%) of bruising, 8 cases (0.72%) of malar edema, 5 cases (0.45%) of temporarily palpable lumps and 2 cases (0.18%) of discoloration at injection site. Bruising/hematoma, swelling/edema, and palpable lumps occurred within 14 days of treatment. Malar edema occurred >2 weeks to 3 years post-treatment, and discoloration occurred at 10 months and 11 months.

A 2019 single-clinic prospective study included 13 patients with thin skin and skin atrophy due to aging and moderate-to-severe levels (Class II and III in Fitzpatrick's Classification) of facial wrinkles. 100% were female, with a mean age of 38.7 years.[32] After the topical application of a 9% lidocaine cream, all patents were injected with 3 cc of diluted PCL (0.5 cc) filler (Ellansé-M) in the dermis; 0.0005 cc per site using an injector. Most patients were followed for 1 year; 3 patients were followed for 4 years. All patients experienced mild swelling for 1 or 2 days, but none of the cases of prolonged swelling lasted more than 5 days. Seven patients (53.8%) experienced ecchymosis on injection sites, especially on thinner skin areas, for 2 or 5 days due to injection using multiple sharp needles on 1000 sites. Histology results indicated:

- At 2 weeks an inflammatory response of numerous macrophages and foreign body giant cells (FBGCs) around the PCL particles; no eosinophils.
- At 1-year, numerous FBGCs, macrophages and monocytes were detected all around the PCL particles. 5 eosinophils were detected in 10 specimen slides. All PCL particles were surrounded by a FBGC.
- At 4 years, all PCL particles were still surrounded by a FBGCs. 3 eosinophils were detected in 10 slides.
- At 2 weeks and 1 year, the PCL particle was approximately 40 microns, smooth on the surface and sphere-shaped. At 4 years, the filler particles decreased, were irregular with rough surfaces and almost all cleaved (split).

Lastly, a 2016 single arm study reported on 58 patients (57 women, 98%; 1 man, 2%), aged 20 to 65 years, undergoing forehead augmentation with Ellansé-M over a 2-year period in a single clinic.[33] The reasons behind forehead contouring treatment were cosmetic: uneven contour (n = 29, 50%), or a concavity due to a prominent brow ridge and relative frontal bone bossing, a flat surface, and volume augmentation (n = 29, 50%). Patients received an injection of botulinum toxin 2 weeks before PCL injection (a 1.1 mL dose of Ellansé-M mixed with 0.19 mL of 2.0% lidocaine HCl solution). Injection-related adverse events included edema and ecchymosis (data not shown).

Systemic Responses

We did not identify any studies investigating systemic responses to PCL as dermal filler.

Overall Quality of Evidence

The evidence base was small, and all studies were low quality. Edema and ecchymosis were reported in 2 (66%) studies, however 1 study did not report occurrence, so we rated the quality of evidence as low. For other local responses and systemic responses (no studies investigating), we rated the quality of evidence as very low.

Meniscus scaffold

3 human studies (3 SRs[34-36]). For further information see Table 7 in Appendix D.

Local Host Responses (human studies)

Studies compared a PCL scaffold (synthetic; Actifit) to a collagen-based scaffold (biologic) for patients undergoing partial meniscectomy due to loss of meniscal tissue due to injury, surgery, or degenerative processes. Studies involved 17% to 47% female patients aged 30 to 37 years, with a follow-up from 24 to 72 months. Overall, the 3 SRs included 18 single arm studies, and 2 nonrandomized comparative studies with 541 patients receiving Actifit.

Extrusion: 1 SR[35] noted that MRI demonstrated PCL scaffold implantation was followed by an increase of coronal meniscal extrusion within 40 months of follow-up, particularly when implanted into the medial knee compartment.

Dislocation, non-integration, and tearing of scaffold: A single arm study included in 1 SR[36] reported on non-integrated scaffold, tear in scaffold, and dislocation of scaffold in 1 (1.9%) patient at 2 year follow-up.

Irregular margins and scaffold size reduction: 3 of 5 studies in 1 SR[34] indicated that the Actifit scaffold tended to form irregular margins and reduce in size over time after 24 months (2 studies) and after 60 months (1 study).

Failure/Reoperation due to pain: Failure definitions vary, but in general refer to the need for reoperation due to pain. 1 SR[34] reported PCL scaffold failure rates from 5% to 32% from 24 to 72 months. Another SR[35] noted PCL scaffold failure in 9.9% of patients at mean 40 months, compared to biologic scaffold failure in 6.7% of patients at mean 44 months.

A single arm study included in 1 SR[36] reported scaffold failure leading to eventual partial knee arthroplasty in 1 (1.9%) patient with 2 year follow-up. This study reported 5 of 6 operations on the lateral meniscus were considered to have a possible or definite relationship with the PCL scaffold.

Chronic pain: 1 SR[36] reported pain in 3 patients (5.8%) at 2 year follow-up.

Stiffness: 2 studies included in 1 SR[34] reported knee stiffness in 2 patients (rates of 4% and 5.3%). 1 patient received reconstruction of the anterior cruciate ligament in addition to PCL scaffold implantation.

Synovitis: 1 study included in 1 SR[34] reported synovitis in 4 (16%) patients with Actifit compared with 1 (3.5%) patient with persistent synovitis with collagen meniscus implant.

Lastly, 3 studies from 1 SR[34] reported non-specified complications in 24 to 72 months follow-up. 3 studies in 2 SRs[34,36] reported no complications or treatment failures for PCL scaffold.

Systemic Responses

We did not identify any studies investigating systemic responses to PCL as meniscus scaffold.

Overall Quality of Evidence

The evidence base was small and mostly consisted of uncontrolled single arm studies. Evidence was mostly inconsistent across studies, so we rated the quality of evidence for all outcomes as very low. The quality of evidence for systemic responses was also rated very low (no studies investigating).

Drug-eluting stent

4 human studies (2 RCTs,[37,38] 1 RCT and registry study,[39] and 1 nonrandomized comparative study[40]). For further information see Table 8 in Appendix D.

Local Host Responses (human studies)

One RCT,[37] the CENTURY II trial, examined 1,123 patients (1,101 in the per-protocol analysis) with ischemic heart disease due to stenotic lesions of coronary arteries treated with either a sirolimus-eluting stent containing bioresorbable PCL (Ultimaster; Terumo) (n = 551 per-protocol) or an everolimus-eluting stent containing a permanent non-PCL polymer (Xience; Abbott Vascular) (n = 550 per-protocol). The study reported the following rates at 9-month follow-up among patients receiving Ultimaster versus Xience: clinically indicated target lesion revascularization (TLR), 2.18% versus 1.64%; in-stent restenosis, 1.27% versus 1.21%; in-segment restenosis, 3.80% versus 2.83%; target vessel (TV)-related myocardial infarction (MI), 1.27% versus 2.18%; target lesion failure (TLF), defined as cardiac death, TV-related MI, or clinically indicated TLR, 4.36% versus 4.91%. No rates differed significantly across groups.

Another RCT,[38] the PAINT trial, examined 274 coronary patients receiving stents containing bioresorbable PCL (paclitaxel-eluting Infinnium®, n = 111, or sirolimus-eluting Supralimus®, n = 106), or bare metal stents (Milennium Matrix®, n = 57); all stents were manufactured by Sahajanand Medical Technologies. The study reported the following rates at 3-year follow-up among patients receiving PCL-containing stents versus bare metal stents: cardiac death or nonfatal MI, 9.0% versus 7.1% (p = ns); TLR, 8.2% versus 28.2% (p <0.01); major adverse cardiac events (defined as cardiac death, MI, or TVR), 14.6% versus 33.3% (p <0.01).

An RCT with an associated registry study[39] examined patients with coronary artery disease receiving either a fully bioresorbable sirolimus-eluting scaffold containing PCL (Xinsorb BRS; Huaan Biotechnology) or a metallic sirolimus-eluting stent not containing PCL (Tivoli; Essen Technology). In the RCT, patients were randomized to receive either Xinsorb (n = 200) or Tivoli (n = 195); in the registry, all patients were scheduled to receive Xinsorb (n = 798). The study reported the following rates at 12-month follow-up from patients in the RCT receiving Xinsorb versus Tivoli: in-device restenosis, 0% versus 0%; TLR, 2.0% versus 5.1%; TV-related MI, 0.5% versus 0%; TLF (defined as cardiac death, TV-related MI, or ischemia-driven TLR), 2.5% versus 5.1%. No rates differed significantly across groups. In the registry, the study reported the following rates at 12-month follow-up: TLR, 0.9%; TV-related MI, 0%; TLF, 0.4%.

A nonrandomized comparative study[40] examined patients who underwent implantation of Ultimaster (n = 26), Xience (n = 21), or Synergy (Boston Scientifics Corp.), an everolimus-eluting stent coated with a biodegradable polymer not containing PCL (n = 30). The study reported that, among patients who received Ultimaster, 2 (8%) experienced major adverse cardiac events (defined as cardiac death, MI, or TVR); in both cases, the event was TVR for in-stent restenosis. No major adverse cardiac events occurred in the other two groups.

Systemic Responses

We did not identify any studies investigating systemic responses to PCL as a constituent of drug-eluting stents.

Overall Quality of Evidence

The evidence base consisted of 4 studies, all with control groups. The 2 largest studies (N>2200 patients) reported no significant difference between groups in all local responses, so we rated the quality of evidence as low. For systemic responses, the quality of evidence was rated very low (no studies investigating).

ECRI Surveillance Data

The most common complication reported within surveillance data for PCL was device failure and malfunction (approximately 50% of all PSO reports) with 98% of those reports related to sutures. PSO reports were split fairly evenly between sutures (56%) and meshes (43%) with a single report related to a fixation device. The most severe events were related to meshes with one leading to a patient's death after suffering a hematoma/hemorrhage during or following a surgical procedure.

Healthcare Technology Alerts returned 24 manufacturer issued alerts. Six alerts were related to mesh products some of which reported a high recurrence rate of post-operative hernia repairs. The remaining alerts were related to sutures many not related to biocompatibility of PCL, but one alerts described premature degradation of the suture. A single alert was related to bone filler, and it was described as compromised product sterility.

Refer to Appendix F for a list of devices that guided our searches of ECRI Surveillance Data.

Patient Safety Organization

Search Results: ECRI PSO identified 86 reports that involved Polycaprolactone materials that occurred between March 2015 and August 2021. Of these reports, 37 related to mesh, 48 related to sutures, 1 related to a fixation device. Among all 86 reports, 42 involved device failure/malfunction followed by 8 episodes of hematoma/hemorrhage, 8 incidents of retained foreign object, and 7 incidents of infection (see Table 3).

Of the reports related to meshes, 7 resulted in no harm, 13 resulted in temporary harm that required intervention (harm score E), 5 resulted in prolonged hospitalization (harm score F), 1 resulted in permanent harm (harm score G), 1 required intervention to sustain the patient's life (harm score H) and one resulted in patient death. The event leading to permanent harm was a hematoma/hemorrhage followed by surgery at an acute care hospital. Based on information provided by the PSO reporter, the cause of the incident that required intervention to sustain life as well as the one that led to patient death was unclear and labeled as a clinical manifestation (see Table 4).

Of the reports related to sutures, 27 resulted in no harm (harm scores B2-D) and 5 resulted in temporary harm that required some intervention. All 5 events that led to temporary harm were described as device failure/malfunction (see Table 4).

Based on the reported circumstances, the harm score of the report related to fixation could not be identified but it involved an identified expired product that did not reach the patient (see Table 4).

All individual PSO event reports are redacted and included in Appendix F.

Table 3: Complications in PCL-related PSO Event Reports

Complication	Fixation	Mesh	Suture	Total
Device failure/malfunction		1	41	42
Hematoma/Hemorrhage		8		8
Retained Foreign Object		3	5	8
Clinical manifestations		8		8

Complication	Fixation	Mesh	Suture	Total
Infection		7		7
Product Expired	1	2	1	4
Iatrogenic Injury		2	1	3
Bowel obstruction		2		2
Venous thromboembolism		1		1
Wound dehiscence		1		1
Perforation		1		1
Mesh erosion		1		1
Total	1	37	48	86

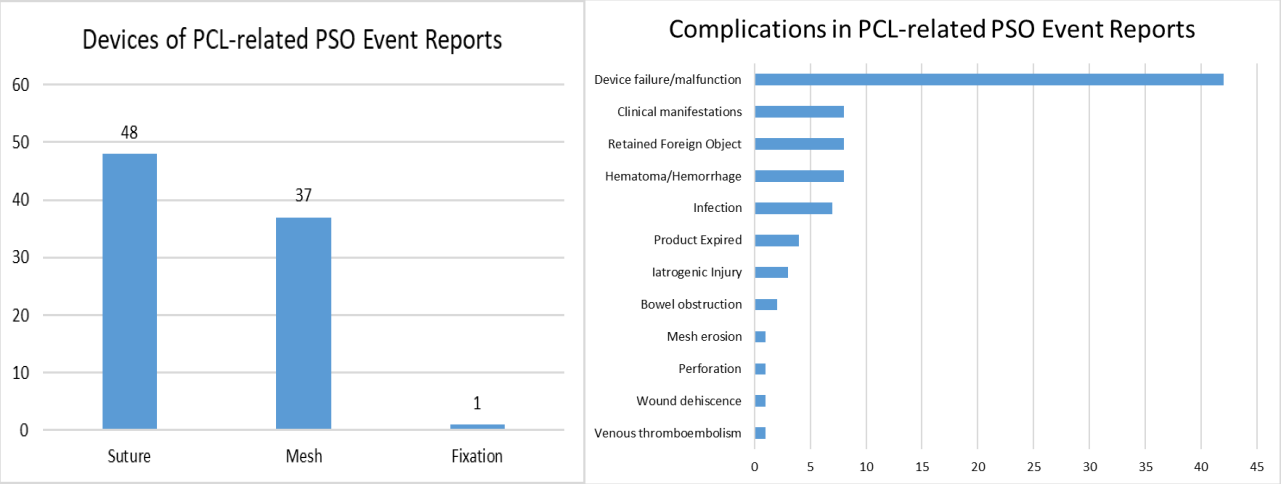


Figure 2: A) Number of PSO report categories by device type, B) Number of PSO reports categorized by event type

Table 4: Harm score associated with PCL-related event reports.

Harm Scores (NCC-MERP)	Harm Scores (NCC-MERP)	Fixation	Mesh	Suture	Total
A	No Error	0	4	3	7
B1	Error, No Harm	0	0	0	0
B2	Error, No Harm	0	0	2	2
C	Error, No Harm	0	2	16	18
D	Error, No Harm	0	5	9	14
E	Error, Harm	0	13	5	18

Harm Scores (NCC-MERP)	Harm Scores (NCC-MERP)	Fixation	Mesh	Suture	Total
F	Error, Harm	0	5	0	5
G	Error, Harm	0	1	0	1
H	Error, Harm	0	1	0	1
I	Error, Death	0	1	0	1
NULL*		1	5	13	19
Total		**1**	**37**	**48**	**86**

**Harm score was not reported*

Accident Investigations

Search Results: Zero investigations were recovered from the accident investigations database.

ECRI Problem Reports

Search Results: The search returned zero reports submitted by ECRI members.

Healthcare Technology Alerts

Search Results: The search returned 24 manufacturer issued alerts describing problems with Polycaprolactone-related devices, including IFU reminders/updates, discontinued product, compromised sterility, mislabeling, high rates of recurrence, products not meeting specifications or retaining strength profiles after implantation, products manufactured with incorrect materials or configurations or damaged equipment, premature degradation, debris, and product contamination, summarized in Table 5.

Table 5: Summary of Regulatory and Manufacturer Alerts

Device Type	# Alerts	Reported Problem
Mesh (FTL – Mesh, Surgical, Polymeric)	5 manufacturer issued	• High recurrence rate after hernia repairs (inguinal, ventral); updated IFU • Distribution discontinued • IFU reminder that outer pouch surface is nonsterile • Compromised sterility
Mesh (OTP – Mesh, Surgical, Synthetic, Urogynecologic, for Pelvic Organ Prolapse, Transvaginally Placed)	1 manufacturer issued	• Distribution discontinued
Suture (GAM – Suture, Absorbable, Synthetic, Polyglycolic Acid)	13 manufacturer issued	• Product does not meet minimum specification requirements • Compromised sterility • Premature degradation • Product contaminated with propylene glycol • Mislabeling • IFU not approved in Canada • Suture damage due to manufacturing equipment
Suture (NEW – Suture, Absorbable, Polydioxanone)	3 manufacturer issued	• Manufactured with wrong material • May not retrain strength after implantation • Product may contain metal debris

Device Type	# Alerts	Reported Problem
Suture (NEW; GAM)	1 manufacturer issued	• Manufactured with incorrect configuration
Bone filler (GXP – Methyl Methacrylate for Cranioplasty)	1 manufacturer issued	• Compromised sterility

Potential Gaps

ECRI surveillance searches reflect mostly acute patient incidents that involved medical devices made of Polycaprolactone. Areas of particular concern involve incidents that result in direct tissue exposure to the material if there is moderate to high-quality evidence of acute or systemic reaction to this exposure, as determined by the systematic review. Topics with very low or low quality of evidence represent areas of potential gaps in the literature. If the literature revealed areas of new concern (e.g., systemic response to long-duration contact) and there is little supporting evidence, these are considered gaps.

Polycaprolactone as a Material

There were no studies that met inclusion criteria for PCL as a material indicating an area of future research.

Mesh

13 high-quality studies investigated PCL mesh in over 2900 patients. Of more than 20 PCL meshes of interest, only 2 PCL meshes (Ultrapro, TIGR Matrix Surgical) were investigated; Ultrapro was examined in 12 (92%) studies. A polypropylene mesh was the comparator in most cases. Most studies focused on hernia repair in middle-aged males with little or no evidence for mesh in other indications, females, and younger populations. Dose was not reported in any study. Several outcomes such as pain, seroma, and hematoma were consistently reported across studies and in agreement with other PCL categories (e.g., suture, packing) so we rated the quality of evidence as moderate. These responses, however, were also reported after use of other meshes (PP, polyester) making the association with PCL unclear. Other local responses (e.g., perioperative bleeding) were rated low quality of evidence due to infrequent or rare reporting. The quality of evidence for systemic responses was rated very low due to no studies reporting.

Sutures

3 human studies compared 3 different PCL sutures (Monocryl, Polysorb, Caprosyn) with non-PCL closure methods (e.g., other sutures, adhesive bandage). Evidence for greater than 35 PCL sutures of interest were not identified. Overall, 468 patients received PCL sutures, but only 1 study each examined cesarean delivery, vaginal cuff closure, and ECTR. Mean age was 31 to 48 years, and follow-up only ranged up to 6 months. Local responses were inconsistent across studies, however all studies had control groups, so the quality of evidence was rated low. Systemic responses were not investigated resulting in a rating of very low quality.

Bone filler

There were no studies that met inclusion criteria for PCL as bone filler indicating an area of future research.

Fixation

There were no studies that met inclusion criteria for PCL for fixation indicating an area of future research.

Packing – ear and nasal

9 high-quality studies examined nasal packing with Nasopore after endoscopic sinus surgery. No evidence was identified for nasal packing with Hemopore or ear packing (Naspore Ear, Otopore). The sinus cavities of 1051 patients (of varying ages) were randomized to PCL packing or non-PCL packing/no packing. Followup was limited to 3 months. Quality of evidence for acute pain, pressure and obstruction/blockage was rated moderate due to the consistency in reporting in higher-quality studies (with overall large enrollment); pain was also in agreement with other device categories (e.g, mesh). For other outcomes (e.g., edema) that were reported in fewer studies, the quality of evidence was rated low. Systemic responses were not investigated resulting in a rating of very low quality.

Dressing

2 human studies examined Suprathel wound dressing (1 of 5 PCL dressings of interest). Of the 14 studies included in the SR, 7 studies were single arm or case reports; only 1 (7%) study enrolled greater than 35 patients. The nonrandomized comparative study only examined 5 patients, each of whom received Suprathel and a nonfibrillar cellulose wound dressing. For local responses, evidence was inconsistent across studies with 50% of individual studies being low quality, so we rated the quality of evidence as very low. Systemic responses were not investigated resulting in a rating of very low quality.

Orthopedic implant

3 human studies examined Artelon CMC spacer in only 142 patients. No evidence for Artelon STT spacer and Artelon MTP spacer was identified. Sample size was 32 to 63 with studies mostly enrolling females (when reported). Outcomes were generally unfavorable, with authors concluding to discontinue use of the implant due to pain and reoperation/explantation rates. For local responses, evidence was inconsistent across studies with most individual studies being low quality, so we rated the quality of evidence as very low. Systemic responses were not investigated resulting in a rating of very low quality.

Nerve capping

There were no studies that met inclusion criteria for PCL for nerve capping indicating an area of future research.

Dermal filler

Ellansé or Ellansé-M dermal filler was investigated in 3 single arm studies enrolling mostly females of Asian descent aged 20 to 68 years. Evidence for 2 other PCL dermal fillers of interest (Miracle H, Miracle L) was not identified. Authors of 1 study (n=780) noted that prolonged edema was associated with higher-volume injection of Ellansé (8.36 mL per treatment), however this study lacked a control group so the association with the material is unclear. Edema and ecchymosis were reported in 2 (66%) studies, however 1 study did not report occurrence, so we rated the quality of evidence as low. For other local responses and systemic responses (no studies investigating), we rated the quality of evidence as very low.

Meniscus scaffold

Overall, 3 SRs including 18 single arm studies and 2 nonrandomized comparative studies examined 541 individuals receiving the same PCL meniscal scaffold (Actifit). Local responses such as extrusion, dislocation, and synovitis were inconsistently reported across studies, so we rated the quality of evidence for all outcomes as very low. The quality of evidence for systemic responses was also rated very low (no studies investigating).

Drug-eluting stent

The evidence base consisted of 4 studies, all with control groups. Overall, 888 patients received various PCL drug-eluting stents including Ultimaster and Xinsorb BRS. The 2 largest studies (n>2200 patients) reported no significant difference between groups in all local responses (e.g., restenosis, TLF), so we rated the quality of evidence as low. Systemic responses were not investigated resulting in a rating of very low quality.

Appendix A. Inclusion/Exclusion Criteria and Quality of Evidence Criteria

Inclusion Criteria

1. English language publication
2. Published between January 2011 and August 2021
3. Human studies (animal studies that provide unique information will also be considered for inclusion)
4. Systematic reviews, randomized controlled trials, cohort studies, case-control studies, cross-sectional studies, case series
5. Studies that evaluate toxicity/biocompatibility of PCL

Exclusion Criteria

1. Foreign language publication
2. Published before January 2011
3. Not a study design of interest (e.g., in vitro lab study, case report, narrative review, letter, editorial)
4. Off-topic study
5. On-topic study that does not address a key question
6. No device or material of interest
7. No relevant outcomes (adverse events or biocompatibility not reported)
8. Study is superseded by more recent or more comprehensive systematic review

Quality of Evidence Criteria

1. **Quality of comparison** – is there evidence from systematic reviews including randomized and/or matched study data and/or randomized or matched individual studies?
2. **Quantity of data** – number of systematic reviews and individual studies providing relevant data, as well as the proportion of included studies that reported a specific outcome.
3. **Consistency of data** – are the findings consistent across studies that report relevant data?
4. Magnitude of effect – what is the likelihood of adverse effects compared to controls (with no device, lower dosage, shorter exposure time), and possibly number of patients likely to have harms.
5. **Directness of evidence** – do human studies isolate the effect of the device (i.e. can the adverse effects be attributed to the device)?
6. Is there evidence of a **dose response or time response** (e.g. adverse effects increase with longer exposure time)?

Appendix B. Search Summary

Strategies crafted by ECRI's medical librarians combine controlled vocabulary terms and free-text words in conceptual search statements that are joined with Boolean logic (AND, OR, NOT).

Most medical bibliographic databases such as Medline and Embase include detailed controlled vocabularies for medical concepts accessible through an online thesaurus. Controlled vocabularies are a means of categorizing and standardizing information. Many are rich ontologies and greatly facilitate information transmission and retrieval. Frequently seen examples of controlled vocabularies include ICD-10, SNOMED-CT, RxNorm, LOINC, and CPT/HCPCS.

Citations in PubMed are indexed with MeSH terms and those in Embase are indexed with terms from EMTREE. These terms are assigned either by a medical indexer or an automated algorithm. Several terms are selected to represent the major concept of the article – these are called "major" headings. This "major" concept can be included in search strategies to limit search retrieval. The syntax in Embase for this is /mj. We have used this convention in our strategies sparingly since indexing is subjective and we are using a sensitive search approach which errs in the direction of comprehensiveness.

Database providers build functionality into their search engines to maximize the usefulness of indexing. One of the most frequently used shortcuts is term explosion. "Exploding" in the context of hierarchical controlled vocabularies means typing in the broadest (root or parent) term and having all the related more specific terms included in the search strategy with a Boolean OR relationship. We use term explosions whenever feasible for efficiency. Feasibility depends on whether you wish to include all of the related specific terms in your strategy. For example, in one of our approaches we explode the Emtree concept mechanics. This explosion automatically added the all the following terms (n = 174) and their associated entry terms (lexical variants and synonyms) to the strategy using an "OR" without the searcher having to type them in. That's one of the major advantages to searching using controlled vocabularies. We don't rely exclusively on controlled vocabulary terms since there are possible limitations such as inconsistent indexing and the presence of unindexed content. That's why we also include free text words in our strategies.

Material: Polycaprolactone (PCL)

Set Number	Concept	Search Statement
1.	**Polycaprolactone (PCL) and derivatives**	'polycaprolactone'/exp OR ('poly NEAR/6 caprolactone*') OR ('polycaprolactone*' OR 'polyglactone*' OR 'poliglecaprone*' OR 'polycaprolate*' OR 'epsiloncaprolactone*' OR 'ecaprolactone*' OR 'sigmacaprolactone*' OR 'oligocaprolactone*' OR 'caproprene*' OR 'polyglecaprone*'):ti,ab
2.	PCL Mesh	('tyrx' OR 'antibacterial envelope' OR 'antibiotic envelope' OR 'antimicrobial envelope' OR 'neuro envelope' OR 'aigisr*' OR 'aigis r*' OR tigrmesh OR (tigr AND mesh) OR flexband OR flexpatch OR ('ultrapro*' AND ('mesh*' OR 'hernia*' OR 'patch*' OR 'plug*')) OR 'physiomesh*' OR 'artisyn*' OR (biomerix AND assure) OR 'gynemesh m' OR 'gynecare prolift m' OR 'sportmesh' OR 'artelon' OR 'mesofol' OR 'vivosorb' OR 'osteoplug*' OR 'osteomesh*'):ti,ab,kw,de,tn,dn
3.	PCL sutures	('artelon' OR 'bondek' OR 'caprolon' OR 'caprosyn' OR 'coated vicryl rapide' OR 'demecaprone' OR 'dexon' OR 'filapron' OR 'mono q' OR 'monocryl' OR 'monoderm' OR 'monoglyde' OR 'monoswift' OR 'novafil' OR 'vascufil' OR 'optime pga' OR 'sinusorb pga' OR 'orthocard' OR 'panacryl' OR 'polyglytone' OR 'polysorb' OR 'quill monoderm' OR 'rexmono' OR 'monofast' OR 'rexsin' OR 'trisorb' OR 'rondek pga' OR 'sharpoint' OR 'stratafix' OR 'surgitie' OR 'unicaprone'):ti,ab
4.	Other PCL devices	('osteopore*' OR 'chronos composite' OR 'chronos strip composite' OR 'smartbone' OR 'swissbone' OR 'craniosorb' OR 'trumatch graft cage' OR 'rotium' OR 'nasopore' OR 'hemopore' OR 'otopore' OR 'neurocap' OR 'neurolac' OR 'polyfit' OR 'suprathel' OR 'phoenix wound matrix' OR 'suprasdrm' OR 'topkin foil' OR 'ellanse*' OR 'actifit' OR 'combo des' OR 'combo plus des' OR 'xinsorb' OR 'ultimaster'):ti,ab,kw,de,tn,dn

Set Number	Concept	Search Statement
5.	PCL Devices: Mesh, packing, and adhesion barrier terms	#1 AND ('adhesion barrier'/exp OR 'adhesion barrier film'/exp OR 'adhesion barrier gel'/exp OR 'anti-adhesion solution'/exp OR 'adhesion'/exp OR 'peritoneum adhesion'/exp OR 'tissue adhesion'/exp OR 'uterus synechia'/exp OR 'anastomotic device'/exp OR 'surgical mesh'/exp OR 'adhes*':ti,ab OR 'adher*':ti,ab OR 'antiadhes*' OR 'anti-adhes*':ti,ab OR 'barrier*':ti,ab OR sealant*:ti,ab OR 'mesh':ti,ab OR 'nasal packing':ti,ab OR 'packing material':ti,ab OR 'nasal splint*':ti,ab)
6.	PCL Devices: Other device terms	#1 AND ('suture'/exp OR 'cardiovascular prosthesis and implant'/exp OR 'orthopedic prostheses, orthoses and implants'/exp OR 'neurological prosthesis and implant'/exp OR 'prostheses and orthoses'/exp OR 'implant'/exp OR 'orthopedic fixation device'/exp OR 'dermal implant'/exp OR 'injectable dermal implant'/exp OR 'plastic surgery implant'/exp OR (prosth* OR implant* OR suture* OR staple OR fixation OR spacer? OR stent* OR 'bioresorbable scaffold*' OR 'nerve cuff*' OR 'nerve cap*' OR 'nerve conduit*' OR 'filler?'):ti,ab)
7.	**Combine sets**	**#2 OR #3 OR #4 OR #5 OR #6**
8.	Limit by language and publication date	#6 AND [english]/lim AND [2011–2021]/py
9.	Limit by publication type	#7 NOT ('book'/it OR 'chapter'/it OR 'conference abstract'/it OR 'conference paper'/it OR 'conference review'/it OR 'editorial'/it OR 'erratum'/it OR 'letter'/it OR 'note'/it OR 'short survey'/it OR 'tombstone'/it)

Material Response

10.		**'biocompatibility'/de OR biocompat* OR tribolog* OR 'bio compat*' OR 'biological* compat*' OR 'biological* evaluation'**
11.		'degradation'/exp OR degrad* OR adsorbable OR split* OR wear OR deteriorat* OR atroph* OR migrat* OR distend* OR distension OR 'delamination'/exp OR delamina* OR leach* OR filter* OR seep* OR evaginat* OR subsidence
12.		Leachable* OR extractable*
13.		(swell* OR shrink* OR contract* OR stretch* OR retract* OR extension OR extend* OR deform* OR creep OR plasticity OR degrad* OR disintegrat* OR fail* OR fragment* OR debond*) NEAR/3 (hydrogel* OR implant* OR prosthes* OR prosthetic* OR injectable* OR putty OR putties OR graft OR device?)
14.		'mechanics'/exp

		[see Emtree explosions section at the end of the strategy]
15.		'device material'/exp/mj
16.		'Biomedical and dental materials'/exp/mj
17.	**Combine sets**	**#10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16**

Host Response

18.		**Host NEAR/2 (reaction* OR response*)**
19.		'toxicity'/exp OR toxic*:ti OR cytotox* OR teratogenic* OR genotox* 'carcinogenicity'/exp OR carcinogen*:ti
20.		'immune response'/exp OR 'immunity'/exp/mj OR 'hypersensitivity'/exp OR 'immunopathology'/exp/mj
21.		(immun*:ti OR autoimmun*:ti OR hypersens*:ti) NOT immunofluorescenc*:ti
22.		'inflammation'/exp OR (inflamm* NEAR/3 (tissue OR macrophage* OR cytokine* OR react* OR respons* OR level* OR sign* OR effect* OR activat* OR local OR inhibit* OR alleviat* OR reduc* OR decreas* OR induce* OR synovial))
23.		'foreign body' OR granuloma* OR 'foreign body'/exp OR 'macrophage'/exp OR 'macrophage*':ti,ab OR fouling OR 'anti-fouling' OR biofilm?
24.		'adhesion'/exp OR 'tissue adhesion'/exp OR 'tissue response' OR 'tissue reaction' OR 'necrosis':de OR 'necrosis':ti,ab
25.		protrude* OR protrus* OR perforat*
26.		'fibrosis'/exp OR 'seroma'/exp OR 'hematoma'/exp OR 'seroma*' OR 'hematoma*' OR 'thrombosis'/exp OR 'thrombosis'/syn OR 'phlebitis'/exp OR 'phlebitis'/syn OR 'skin irritation'/exp OR 'pruritus'/exp OR 'pruritus' OR itch*:ti,ab
27.	**Combine sets**	**#18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26**

Other Combinations

28.	PCL + Material Response + Host Response	**#9 AND #17 AND #27**
29.	**PCL general devices + Host response**	(#5 OR #6) AND #9 AND #27
30.	**Combine sets**	#28 OR #29
31.	**PCL systematic reviews**	#9 AND ('systematic review'/de OR 'meta analysis'/de OR ((meta NEAR/2 analy*):ti) OR 'systematic review':ti)
31	**Combine all**	**#30 OR #31**

Example Embase Explosion

Mechanics/exp

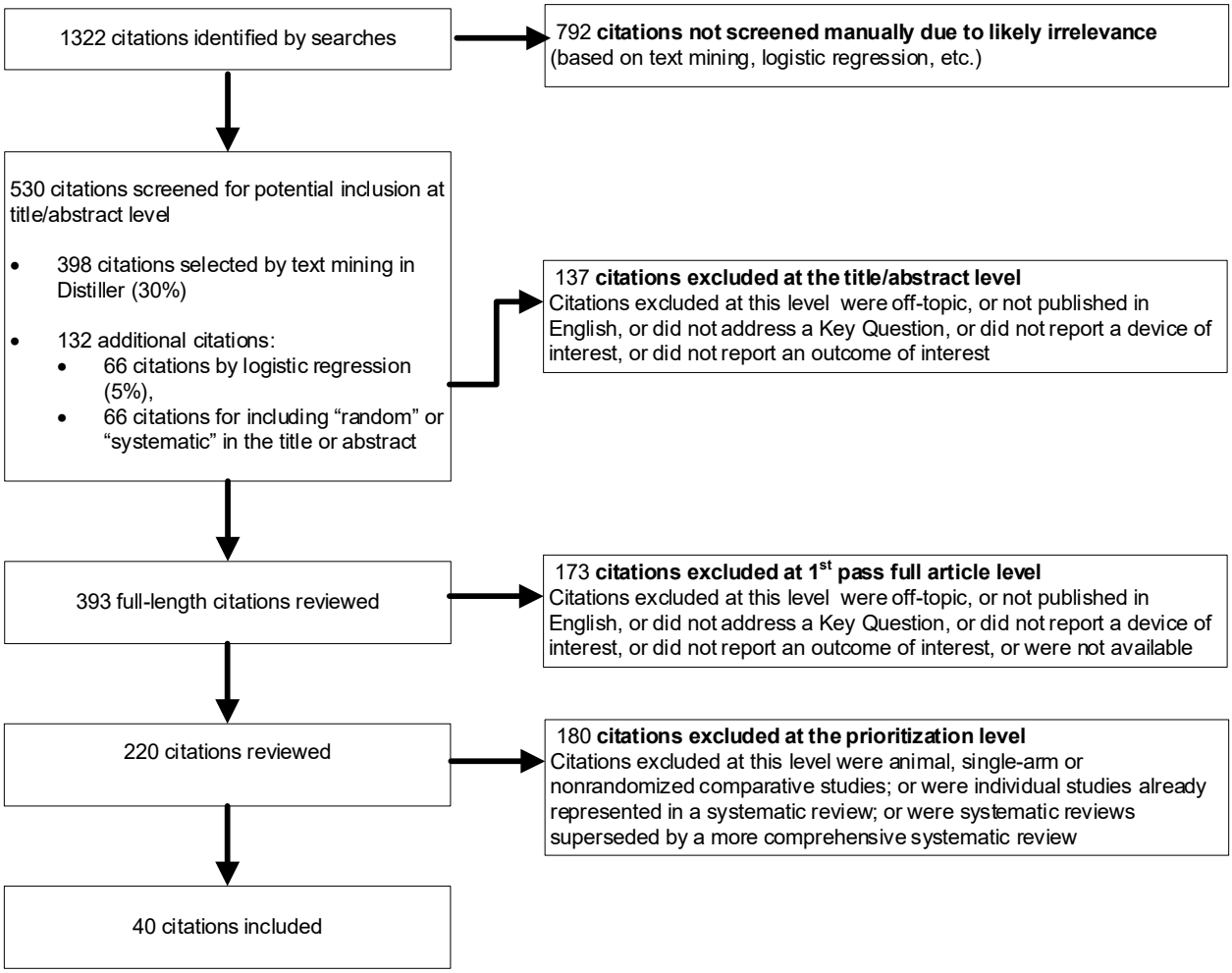
- Biomechanics
- Compliance (physical)
    - Bladder compliance
    - Blood vessel compliance
        - Artery compliance
        - Vein compliance
    - Heart muscle compliance
        - Heart left ventricle compliance
        - Heart ventricle compliance
    - Lung compliance
- Compressive strength
- Dynamics
    - Compression
    - Computational fluid dynamics
    - Decompression
        - Explosive decompression
        - Rapid decompression
        - Slow decompression
    - Gravity
        - Gravitational stress
        - Microgravity
        - Weight
            - Body weight
                - Birth weight
                    - High birth weight
                    - Low birth weight
                        - Small for date infant
                        - Very low birth weight
                            - Extremely low birth weight
            - Body weight change
                - Body weight fluctuation
                - Body weight gain
                    - Gestational weight gain
                - Body weight loss

                - Emaciation
            - Body weight control
            - Fetus weight
            - Ideal body weight
            - Lean body weight
            - Live weight gain
        - Dry weight
        - Fresh weight
        - Molecular weight
        - Organ weight
            - Brain weight
            - Ear weight
            - Heart weight
            - Liver weight
            - Lung weight
            - Placenta weight
            - Spleen weight
            - Testis weight
            - Thyroid weight
            - Uterus weight
        - Seed weight
        - Tablet weight
        - Thrombus weight
    - Weightlessness
- Hydrodynamics
    - Hypertonic solution
    - Hypotonic solution
    - Isotonic solution
    - Osmolality
        - Hyperosmolality
        - Hypoosmolality
        - Plasma osmolality
        - Serum osmolality
        - Urine osmolality
    - Osmolarity
        - Blood osmolarity
        - Hyperosmolarity
        - Hypoosmolarity
        - Plasma osmolarity
        - Serum osmolarity
        - Tear osmolarity
        - Urine osmolarity
    - Osmosis
        - Electroosmotic
        - Osmotic stress
            - Hyperosmotic stress
            - Hypoosmotic stress
- Photodynamics
    - Photoactivation
        - Photoreactivation
    - Photodegradation
    - Photoreactivity
        - Photocytotoxicity
        - Photosensitivity
        - Photosensitization

                - Phototaxis
                - Phototoxicity
            - Photostimulation
        - Proton motive force
        - Shock wave
            - High-energy shock wave
        - Stress strain relationship
        - Thermodynamics
            - Adiabaticity
            - Enthalpy
            - Entropy
- Elasticity
    - Viscoelasticity
    - Young modulus
- Force
- Friction
    - Orthodontic friction
- Hardness
- Kinetics
    - Adsorption kinetics
    - Flow kinetics
        - Electroosmotic flow
        - Flow rate
        - Gas flow
        - Laminar airflow
        - Laminar flow
        - Powder flow
            - Angle of repose
            - Hausner ration
        - Pulsatile flow
        - Shear flow
        - Thixotropy
        - Tube flow
        - Turbulent flow
        - Vortex motion
        - Water flow
    - Motion
        - Coriolis phenomenon
        - Rotation
        - Vibration
            - Hand arm vibration
            - High frequency oscillation
            - Oscillation
            - Oscillatory potential
            - Whole body vibration
    - Velocity
        - Acceleration
        - Deceleration
        - Processing speed
        - Wind speed
- Mass
    - Biomass
        - Fungal biomass
        - Immobilized biomass
        - Microbial biomass

    - Body mass
    - Bone mass
    - Dry mass
    - Fat free mass
    - Fat mass
    - Heart left ventricle mass
    - Kidney mass
- Materials testing
- Mechanical stress
    - Contact stress
    - Contraction stress
    - Shear stress
    - Surface stress
    - Wall stress
- Mechanical torsion
- Molecular mechanics
- Plasticity
- Pliability
- Quantum mechanics
    - Quantum theory
- Rigidity
- Torque
- Viscosity
    - Blood viscosity
        - Plasma viscosity
    - Gelatinization
    - Shear rate
    - Shear strength
    - Shear mass
    - Sputum viscosity
    - Viscoelasticity

Appendix C. Study Flow Diagram



1,322 Citations were identified by searches, of which:

1. 792 citations were not screened manually due to likely irrelevance (based on text mining, logistic regression, etc.)

2. The remaining 530 citations were screened for potential inclusion at title/abstract level (398 citations were selected by text mining in Distiller (30%); and 132 additional citations were selected - 66 by logistic regression (5%) and 66 for including "random" or "systematic" in the title or abstract)

    a. 137 citations were excluded at the abstract level. Citations excluded at this level were off-topic, or not published in English, or did not address a Key Question, or did not report a device of interest, or did not report an outcome of interest.

    b. The remaining 393 full length citations were reviewed, of which:

        i. 173 citations were excluded at 1st pass full article level, Citations excluded at this level were off-topic, or not published in English, or did not address a Key Question, or did not report a device of interest, or did not report an outcome of interest, or were not available.

        ii. The remaining 220 citations were reviewed, of which:

1. 180 citations were excluded at the prioritization level. Citations excluded at this level were animal, single-arm or nonrandomized comparative studies; or were individual studies already represented in a systematic review; or were systematic reviews superseded by a more comprehensive systematic review.

2. 40 citations were included.

Appendix D. Evidence Tables

Table 1: Mesh - Health Effect (In Vivo) Human Studies

Local Response/Toxicity

1. Source Citation: Hansson et al. 2021[3]

Study Design: RCT

Device or Material: TIGR Matrix Surgical Mesh (Novus Scientific, Uppsala Sweden; synthetic mesh) vs. Veritas Collagen Matrix (Synovis Surgical Innovations; biological mesh comprised of non-crosslinked bovine pericardium)

Contact Duration: 12 months

Dose: NR

Frequency/Duration: Single Administration

Response: Seroma Formation

Patient characteristics (gender, mean age): 100% females, median 42 (range 25 to 65 years).

Number per group: 24 breasts (48 total breasts, 24 patients used as own controls); bilateral mastectomy and immediate breast reconstruction.

Observations on adverse effects: Seroma formation was significantly lower with TIGR (2 (8.3%) vs. 9 (38%); p=0.01).

Timing of adverse effects: Seroma occurred 1 and 2 weeks after mastectomy.

Factors that predict response: NR

2. Source Citation: Bakker et al. 2020[1]

Study Design: Systematic review

Device or Material: Ultrapro LWM vs. Prolene (polypropylene mesh) or PP mesh (device NR)

Contact Duration: 1 year (2 studies), 3 years (1 study)

Dose: g/m2: Ultrapro 28; Prolene 82; PP 90 and 80 to 100

Frequency/Duration: NR

Response:
- Chronic pain
- Feeling of a foreign body
- Hernia recurrence

Patient characteristics (gender, mean age): 92% to 100% male, range 56 to 61 years.

Number per group: 3 RCTs compared Ultrapro LWM with Prolene (1 study), and PP (2 studies). Patients undergoing inguinal hernia repair.

Demetrashvili 2014 at 3 years: 113 Ultrapro, 113 Prolene.
Rutegard 2018 at 1 year: 194 Ultrapro, 197 PP.
Bona 2018 at 1 year: 411 Ultrapro, 397 PP.

Observations on adverse effects:

Hernia recurrence rates ranged from 0% to 2.1% with Ultrapro, 0% to 2.2% with PP, and were 0.9% with Prolene. No significant differences were reported for recurrence.

Demetrashvili at 3 years: 1/96 (1%) Ultrapro, 1/102 (0.9%) Prolene; risk ratio (RR) 1.06, 95% CI: 0.07 to 16.75.
Rutegard at 1 year: 4/185 (2.1%) Ultrapro vs. 4/178 (2.2%) PP; RR 0.96, 95% CI: 0.24 to 3.79.

Bona at 1 year: 0/325 Ultrapro, 0/317 PP.

Feeling of a foreign body was reported in 2 studies. Rates were 1% and 14% with Ultrapro, 8.8% with Prolene, and 23% with PP. Both studies showed significant differences favoring LWM for this outcome.

Demetrashvili at 3 years: 1/96 (1%) Ultrapro, 9/102 (8.8%) Prolene; RR 0.12, 95% CI: 0.02 to 0.91.
Rutegard at 1 year: 21/149 (14%) Ultrapro, 34/144 (23.6%) PP; RR 0.60, 95% CI: 0.36 to 0.98.

2 studies reported no significant differences in any chronic pain.
Demetrashvili at 3 years: 2/96 Ultrapro, 5/102 Prolene; RR 0.42, 95% CI: 0.08 to 2.14.
Bona at 1 year: 80/325 Ultrapro, 83/317 PP; RR 0.94, 95% CI: 0.72 to 1.23.

1 study reported no significant differences in severe chronic pain.
Bona at 1 year: 2/325 (0.6%) Ultrapro, 3/317 (0.9%) PP; RR 0.65, 95% CI: 0.11 to 3.87.
Authors were confident that mesh type accounts for at least a great part of the influence for chronic pain.

Timing of adverse effects: 1 year, 3 years, 5 years.

Factors that predict response: NA

3. Source Citation: Wong et al. 2018[4]

Study Design: RCT

Device or Material: Ultrapro (Ethicon), a LWM made of PP and PCL vs. Parietex (Tyco Healthcare), a HWM made of polyester

Contact Duration: Mean 20.3 months (range, 12 to 34 months)

Dose: Weight: 28 g/m2, thickness 0.5 mm, pore size: 3-4mm

Frequency/Duration: Single administration

Response:
- Discomfort sensation
- Foreign body sensation
- Hernia recurrence
- Seroma formation
- Urinary retention

Patient characteristics (gender, mean age): 96% male, age range 27 to 81 years.

Number per group: 39 Ultrapro, 38 Parietex analyzed; 85 patients undergoing laparoscopic inguinal hernia repair were randomized.

Observations on adverse effects:
Seroma formation was significantly lower with Ultrapro (2 vs. 9; p=0.02).
Urinary retention (3 vs. 0; p=0.08) and recurrence (2 vs. 0; p=0.15) only occurred with Ultrapro. No significant difference was also reported for foreign body sensation, and discomfort sensation in different positions at 12 months.
Foreign body sensation (graded on a scale from 0 (least discomfort) to 5 (most severe discomfort)(mean (range)):
Resting: 0.05 (0-1) Ultrapro, 0 Parietex; p=0.16
From lying to sitting: 0.15 (0-2) Ultrapro, 0.11 (0-2) Parietex; p=0.705
Exercise: 0.1 (0-2) Ultrapro, 0 Parietex; p=0.08
Discomfort sensation:
Resting: 0.05 (0-2) Ultrapro, 0 Parietex; p=0.32
Coughing: 0 each arm
From lying to sitting: 0.1 (0-2) Ultrapro, 0 Parietex; p=0.16
Exercise: 0.18 (0-3) Ultrapro, 0.05 (0-1) Parietex; p=0.61

Timing of adverse effects: Hernia recurrence occurred at 9 months and 12 months.

Factors that predict response: NR

4. Source Citation: Burgmans et al. 2016[5]

Study Design: RCT

Device or Material: Ultrapro (Ethicon, Johnson & Johnson, Amersfoot, The Netherlands), a LWM vs. Prolene (Ethicon, Johnson & Johnson Company, Amersfoot, The Netherlands), a HWM

Contact Duration: 1 year (n=894), 2 years (n=867)

Dose: Weight: 55 g/m2 after absorption of PCL 28 g/m2; 10 cm x 15 cm with large pores (3-4 mm)

Frequency/Duration: Single administration

Response:
- Discomfort
- Foreign body feeling
- Hernia recurrence
- Postoperative pain (clinically relevant NRS 4-10, any pain NRS 1-10)
- Sexual-related pain
- Testicular pain

Patient characteristics (gender, mean age): 100% male, median 55 (range 18 to 94)

Number per group: 440 LWM (Ultrapro), 427 HWM (Prolene) at 2 years

Observations on adverse effects:
Clinically relevant postoperative pain (NRS 4-10) was significantly higher with Ultrapro at 1 and 2 years.
1 year: 13 (2.9%) Ultrapro vs. 3 (0.7%) Prolene; p=0.01.
2 years: 13 (3.0%) Ultrapro vs. 4 (0.9%) Prolene; p=0.03.
Any postoperative pain (NRS 1-10) was increased with Ultrapro at 2 years vs 1 year:
1 year: 52 (11.5%) Ultrapro, 48 (10.9%) Prolene
2 years: 65 (14.8%) Ultrapro, 47 (11%) Prolene

No significant difference was reported for foreign body feeling in the groin at 1 year (60 (13.8%)) Ultrapro, 54 (12.2%) Prolene; p=0.49) and 2 years (percent's unchanged). "No major differences" were reported for testicular pain, and sexual-related pain and discomfort (data not shown). Hernia recurrences were similar at 3 months (4 (0.4%) in each arm), higher (significance not reported) with Ultrapro at 1 year (8 (1.7%) vs. 3 (0.6%) Prolene), and significantly higher with Ultrapro at 2 years (13 (2.7%) vs. 4 (0.8%) Prolene; p=0.03). Multivariate analysis indicated that Ultrapro was associated with a significantly higher recurrence rate at 2 years (OR 3.30, 95% CI: 1.06 to 10.29; p=0.04), as well as associated with significantly more relevant pain at 1 year (OR 3.96, 95% CI: 1.10 to 14.23; p=0.04).

Timing of adverse effects: 1 and 2 years.

Factors that predict response: NR

5. Source Citation: Muysoms et al. 2016[6]

Study Design: RCT

Device or Material: Ultrapro (Ethicon, Inc. Johnson and Johnson, Somerville, NJ) vs. NONMESH

Contact Duration: 24 months

Dose: Width 7.5 cm

Frequency/Duration: Single administration

Response:
- Abdominal wall pain
- Hematoma
- Partial dehiscence
- Seroma

Patient characteristics (gender, mean age): 8% females, 72 years.

Number per group: 56 Mesh, 58 Nonmesh; patients undergoing elective abdominal aortic aneurysm repair through a midline laparotomy. Prophylactic mesh-augmented reinforcement with Ultrapro mesh or conventional laparotomy closure with sutures (Nonmesh).

Observations on adverse effects:
No intraoperative complications were observed in either group. Operative morbidity with Ultrapro (n=56) included partial dehiscence (1), seroma (2), and hematoma (2) which did not occur with Nonmesh.

Presence of abdominal wall pain at 1 year (48 Mesh, 47 Nonmesh assessed)
No pain: 46 (96%) Ultrapro, 42 (90%) Nonmesh
Infrequent mild pain: 1 (2%) Ultrapro, 2 (4%) Nonmesh
Frequent mild pain: 0 Ultrapro, 3 (6%) Nonmesh
Serious pain interfering with daily life: 1 (2%) Ultrapro, 0 Nonmesh

Presence of abdominal wall pain at 2 years (48 Mesh, 41 Nonmesh assessed)
No pain: 47 (98%) Ultrapro, 40 (98%) Nonmesh
Infrequent mild pain: 0 Ultrapro, 1 (2%) Nonmesh
Frequent mild pain: 1 (2%) Ultrapro, 0 Nonmesh
Serious pain interfering with daily life: 0 both arms

Timing of adverse effects: Operative morbidity was within 30 days of operation. Chronic pain was assessed at 12 and 24 months.

Factors that predict response: NR

6. Source Citation: Nikkolo et al. 2016[7] and Nikkolo 2014[8]

Study Design: RCT

Device or Material: Ultrapro mesh (UM; (Ethicon, Hamburg, Germany) vs. Optilene LP mesh (OM; B. Braun, Rubi, Spain), a polypropylene mesh

Contact Duration: 6 months[8] and 3 years[7]

Dose: Weight: 28 g/m2 UM, 36 g/m2 OM; pore size 3-4 mm UM, 1 mm OM; size: both 4.5 x 10 cm

Frequency/Duration: Single Administration

Response:
- Chronic pain
- Foreign body sensation
- Hematoma
- Postoperative pain
- Seroma

Patient characteristics (gender, mean age): 82% male Ultrapro, 95% male Optilene LP; 57.4±15 Ultrapro, 60.7±13.8 Optilene LP

Number per group: 65 Ultrapro (UM), 63 Optilene LP (OM); 67 each arm from 1 week to 6 months. Undergoing inguinal hernia repair.

Observations on adverse effects: Hematoma occurred in 18 patients (9 UM, 9 OM) while seroma occurred in 3 patients (1 UM, 2 Optilene LP).

Postoperative pain at 1 week
None: 7 (10.5%) UM, 13 (19.4%) OM
Mild (1-10): 2 (3%) UM, 5 (7.5%) OM
Moderate (11-50): 38 (56.7%) UM, 34 (50.8%) OM
Severe (>50): 20 (30%) UM, 15 (22.4%) OM

Postoperative pain at 1 month
None: 32 (47.8%) UM, 39 (54.9%) OM

Mild (1-10): 3 (4.5%) UM, 8 (11.9%) OM
Moderate (11-50): 27 (40.3%), 16 (23.9%) OM
Severe (>50): 5 (7.5%), 4 (6%) OM

Postoperative pain at 6 months
None: 36 (53.7%) UM, 44 (65.7%)
Mild (1-10): 9 (13.4%) UM, 5 (7.5%) OM
Moderate (11-50): 18 (26.9%) UM, 16 (23.9%) OM
Severe (>50): 4 (6%) UM, 2 (3%) OM

Significantly higher chronic pain at 3 year followup with UM (22 (33.9%) UM, 10 (15.9%) OM; p=0.02). Of these individuals, 6/34 (17.7%) UM, 3/40 (7.5%) OM did not report pain prior to 3 year f/u.

Pain during different activities at 3 year f/u:
Groin pain at rest: 5 (7.7%) UM, 1 (1.6%) OM; p=0.20
Groin pain when coughing: 0 UM, 2 (3.2%) OM; p=0.24
Groin pain when rising from lying to sitting: 5 (7.7%) UM, 4 (6.3%) OM; p=0.99
Groin pain during physical activity: 18 (27.7%) UM, 9 (14.3%) OM; p=0.08

Foreign body in the inguinal region at 6 months (67 each arm)
47.8% UM, 31.3% OM; p=0.052
Risk ratio for foreign body feeling was 1.52 (95% CI: 1.00 to 2.37).

Foreign body in the inguinal region at 3 years
15 (23.1%) UM, 10 (15.9%) OM; p=0.37; Risk ratio for foreign body feeling was 1.45 (95% CI: 0.72 to 2.97).

Foreign body experienced in the inguinal region at 6 months but not at 3 years
20/31 (64.5%) UM, 12/19 (63.2%) OM

Foreign body only experienced in the inguinal area at 3 years
4/34 (11.8%) UM, 3/44 (6.8%) Optilene LP

Timing of adverse effects: Wound hematoma occurred at day 7 postoperatively. Seroma and postoperative pain were assessed at 1 week and 1 month. Chronic pain and foreign body reaction were assessed at 6 months and 3 years.

Factors that predict response: NR

7. Source Citation: Burgmans et al. 2015[9]

Study Design: RCT

Device or Material: Ultrapro (Ethicon, Johnson & Johnson) vs. Prolene (also Ethicon)

Contact Duration: 3 months

Dose: Weight: 55 g/m2 Ultrapro [after absorption of PCL at 28 g/m2], 80 g/m2 Prolene; pore size 3-4 mm Ultrapro, 0.8-1.2 mm Prolene; size: both 10 x 15 cm

Frequency/Duration: Single administration

Response:
- Acute pain
- Chronic relevant pain (3 months)
- Foreign body sensation
- Hematoma
- Perioperative bleeding
- Postoperative bleeding
- Recurring hernia

Patient characteristics (gender, mean age): 100% male; median 55 (range 18-94)

Number per group: 463 Ultrapro, 454 Prolene; patients undergoing endoscopic totally extraperitoneal (TEP) hernia repair

Observations on adverse effects:
Perioperative bleeding occurred in 5 (1.1%) patients with Ultrapro, and 7 (1.5%) patients with Prolene. Postoperative bleeding occurred in 4 (0.9%) patients with Ultrapro, and 5 (1.1%) patients with Prolene. Hematoma occurred similarly (12.7% Ultrapro, 12.1% Prolene).

Pain at day 1
Mild pain: 49.0% Ultrapro, 44.2% Prolene
Moderate pain: 35.9% Ultrapro, 41.5% Prolene
Severe pain: 9.8% Ultrapro, 7.9% Prolene
No pain: 5.2% Ultrapro, 6.3% Prolene; p=0.23

Pain at 1 week
Mild pain: 58.4% Ultrapro, 59.2% Prolene
Moderate pain: 13.1% Ultrapro, 13.3% Prolene
Severe pain: 1.3% Ultrapro, 0.7% Prolene
No pain: 27.2% Ultrapro, 26.8% Prolene; p=0.81

Pain at 6 weeks
Mild pain: 26.1% Ultrapro, 23.5% Prolene
Moderate pain: 3.1% Ultrapro, 2.4% Prolene
Severe pain: 0.7% Ultrapro, 0.2% Prolene
No pain: 70.2% Ultrapro, 73.9% Prolene; p=0.50

Chronic pain at 3 months
Chronic relevant pain (NRS 4-10) was reported in 9 (2%) patients with Ultrapro, and 4 (0.9%) patients with Prolene (p=0.17).

- Any pain (NRS>0): 18.6% Ultrapro, 19.6% Prolene; p=0.65
- Mild pain (NRS 1-3): 16.7% Ultrapro, 18.7% Prolene
- Moderate pain (NRS 4-7): 6 (1.3%) Ultrapro, 3 (0.7%) Prolene
- Severe pain (NRS 8-10): 3 (0.7%) Ultrapro, 1 (0.2%) Prolene
- No pain (NRS 0): 81.3% Ultrapro, 80.4% Prolene; p=0.48

Multivariate analysis indicated that mesh type was not a predictor of pain after 3 months (OR 0.91, 0.65 to 1.28; p=0.60).

Foreign body sensation at 3 months was similar (20% Ultrapro, 17.6% Prolene; p=0.56).
Recurrent hernia was reported in 2 (0.4%) patients in each arm.

Timing of adverse effects: Bleeding and hematoma were measured postoperatively. Recurrent hernia was detected after 2-3 months. Pain was assessed at 1 week, 6 weeks, and 3 months. Foreign body sensation was assessed at 3 months.

Factors that predict response: NR

8. Source Citation: Okulu et al. 2013[10]

Study Design: RCT

Device or Material: Ultrapro mesh vs. Vypro mesh vs. Prolene light mesh; all synthetic

Contact Duration: 4 years

Dose: NR

Frequency/Duration: Single administration

Response:

- De novo urgency
- Incontinence
- Suture granuloma
- Urine retention
- Vaginal erosion

Patient characteristics (gender, mean age): 100% female, 50 years.

Number per group: 48 Ultrapro (Group II), 46 Vypro (Group I), 47 Prolene light mesh (Group III); individuals with stress incontinence undergoing sling surgery

Observations on adverse effects:
Vaginal erosion, suture granuloma, incontinence, and de novo urgency were significantly lower with Ultrapro versus Vypro or Prolene. No significant difference was reported for urine retention.

Vaginal erosion (extrusion): 1 (2.08%) Group II, 2 (4.34%) Group I, 2 (4.25%) Group III; p=0.024 (Group II versus Group I and Group III)

Suture granuloma: 1 (2.08%) Group II, 3 (6.52%) Group I, 3 (6.38%) Group III; p=0.024

Urine retention: 2 (4.16%) Group II, 2 (4.34%) Group I, 2 (4.25%) Group III; p=0.08

Incontinence: 1 (2.08%) Group II, 4 (8.69%) Group I, 4 (8.51%) Group III; p=0.018

De novo urgency: 2 (4.16%) Group II, 5 (10.86%) Group I, 4 (8.51%) Group III; p=0.028

Timing of adverse effects: Urine retention resolved by mean 10.6 days. Extrusion developed at a mean of 12.3 months. Incontinence was measured 48 months postoperative.

Factors that predict response: NR

9. Source Citation: Bury et al. 2012[11]

Study Design: RCT

Device or Material: Ultrapro mesh (Ethicon, Hamburg, Germany) vs. Prolene (also Ethicon)

Contact Duration: Median 62 months (range 57 to 66)

Dose: NR

Frequency/Duration: Single administration

Response:
- Acute pain
- Chronic pain
- Hernia recurrence

Patient characteristics (gender, mean age): 100% male, age NR.

Number per group: 195 Ultrapro, 161 Prolene; patients undergoing inguinal hernioplasty.

Observations on adverse effects:
Short-term postoperative pain was reported less frequently with LWM (N not reported). No significant difference was reported for recurrence rate (1.9% Ultrapro vs. 0.6% Prolene; p=0.493) or chronic pain (5 (2.5%) Ultrapro, 4 (2.4%) Prolene) at 5 years. Multivariate analysis indicated that mesh type was significantly associated with postoperative pain.

Timing of adverse effects: Short-term postoperative pain was measured at 3 months.

Factors that predict response: NR

10. Source Citation: Currie et al. 2012[2]

Study Design: Systematic review

Device or Material: Ultrapro vs. Prolene (HWM)

Contact Duration: 12 months

Dose: NR

Frequency/Duration: NR

Response:
- Acute pain
- Chronic pain
- Hernia recurrence
- Seroma

Patient characteristics (gender, mean age): NR

Number per group: 2 RCTs, total N 1002 (n=402 in Chowbey 2010, n=600 in Bittner 2011); N per arm NR. Inguinal hernia repair.

Observations on adverse effects:
Both studies reported no significant difference in development of recurrence.
Bittner 2011: RD -0.00, 95% CI: -0.01 to 0.01.
Chowbey 2010: RD 0.02, 95% CI: -0.00 to 0.05.

Both studies reported no significant difference in development of chronic pain after 1 year.
Bittner 2011: RD -0.02, 95% CI: -0.05 to 0.01.
Chowbey 2010: RD -0.03, 95% CI: -0.07 to 0.00.

1 study reported no significant difference in postoperative pain (7 days).
Chowbey 2010: SMD -0.06, 95% CI: -0.25 to 0.14

Both studies reported no significant difference in development of postoperative seroma.
Bittner 2011: RD 0.04, 95% CI: -0.04 to 0.12
Chowbey 2010: RD -0.02, 95% CI: -0.09 to 0.06

Timing of adverse effects: 7 days for acute pain. 12 months for chronic pain, hernia recurrence, and seroma.

Factors that predict response: NR

11. Source Citation: Magnusson et al. 2012[12]

Study Design: RCT

Device or Material: UltraPro Hernia System (UHS®, Ethicon, Norderstedt, Germany) vs. Prolene Hernia System (PHS®, also Ethicon) vs. Lichtenstein technique

Contact Duration: 12 months

Dose: NR

Frequency/Duration: Single administration

Response:
- Foreign body sensation
- Hematoma
- Ischemic orchitis
- Neuralgia
- Recurrence

Patient characteristics (gender, mean age): 100% male, mean age 58 to 60 between 3 arms

Number per group: 102 UHS, 99 PHS, 108 Lichtenstein; undergoing primary open unilateral hernia repair

Observations on adverse effects:
Up to 30 days
Hematoma: 1 UHS, 3 PHS, 5 Lichtenstein
Ischemic orchitis: 1 each UHS and PHS

30 days to 12 months
Recurrence: 1 each arm
Hematoma: 1 each UHS and PHS

Foreign body sensation: 3 each arm
Neuralgia: 2 each UHS and Lichtenstein

Timing of adverse effects: Up to 30 days, 30 days to 12 months.

Factors that predict response: NR

12. Source Citation: Rickert et al. 2012[13]

Study Design: RCT

Device or Material: Ultrapro partly absorbable mesh (Johnson and Johnson) vs. PP non-absorbable Optilene® Mesh Elastic (B. Braun Aesculap)

Contact Duration: 21 days and 6 months

Dose: Both meshes were 30 x 30 cm; weight: 65 g/m2 after absorption of PCL, weight 28 g/m2 vs. 48 g/m2 for Optilene; pore size: 1.9 -2.2 mm Ultrapro, 2.9-3.2 mm Optilene

Frequency/Duration: Single Administration

Response:
- Hematoma
- Pain
- Seroma formation

Patient characteristics (gender, mean age): NR, mean age 61.6 Ultrapro, 63.2 Optilene.

Number per group: 39 PCL, 41 PP; patients undergoing incisional hernia repair.

Observations on adverse effects: Overall complication rate was similar. At 21 days, more seroma formation (21.6% vs. 17.1%) but less minor hematoma was detected with PCL (16.2% vs. 25.7%). At 6 months, seroma was still detected in 2.94% with PCL, and 6.45% of patients with PP. No hernia recurrence was reported although the authors noted that most recurrences occur after 6 months. Pain was similar in both groups at all followup (preoperatively, 21 days and 6 months postoperatively). The lowest pain score was observed at 6 months (0.47 PCL, 0.52 PP). Patients receiving PCL showed a constant pain score throughout the observation period with a slight improvement at the end of the observation period (1.00 to 0.47) while patients receiving PP mesh showed an improvement from preoperative to postoperative (1.72 to 0.52).

Timing of adverse effects: 21 days and 6 months.

Factors that predict response: NR

cm: centimeters; g/m^2: grams per square meter; HWM: heavyweight mesh; LWM: lightweight mesh; NR: not reported; NRS: Numeric rating scale; PCL: polycaprolactone; PP: polypropylene; RCT: randomized controlled trial; RD: risk difference; SMD: standardized mean difference

Table 2: Sutures - Health Effect (In Vivo) Human Studies

Local Response/Toxicity

1. Source Citation: Buresch et al. 2017[14]

Study Design: RCT

Device or Material: Monocryl suture (PCL) vs. 4-0 polyglactin 910 suture (non-PCL)(manufacturers NR)

Contact Duration: 30 days

Dose: Size: 3-0 monofilament PCL suture vs. 4-0 braided non-PCL suture

Frequency/Duration: Single administration (subcuticular closure of Pfannenstiel skin incision for cesarean)

Response:

- Hematoma
- Seroma
- Wound separation

Patient characteristics (gender, mean age): 100% female; Poliglecaprone 25 (31.4±5.4 years); Polyglactin 910 (31.2±5.4 years). Patients undergoing cesarean delivery through a Pfannenstiel skin incision followed by subcuticular closure.

Number per group: Poliglecaprone 25 (Monocryl) (n=263); Polyglactin 910 (n=257).

Observations on adverse effects:
Hematoma (RR 0.41, 95% CI: 0.04 to 4.49): 1 (0.4%) Poliglecaprone 25; 2 (0.9%) Polyglactin 910.
Seroma (RR 0.41, 95% CI: 0.04 to 4.49): 1 (0.4%) Poliglecaprone 25; 2 (0.9%) Polyglactin 910.
Wound separation of 1 cm or greater in length (RR 0.82, 95% CI: 0.31 to 2.15): 8 (3.0%) Poliglecaprone 25; 8 (3.7%) Polyglactin 910.
Poliglecaprone 25 suture was associated with 40% reduction in the rate of wound complications when compared with polyglactin 910 suture.

Timing of adverse effects: 30-day post-cesarean outpatient visit.

Factors that predict response: NR. Authors speculate that lack of braiding allows for increased infection resistance.

2. Source Citation: Cong et al. 2016[15]

Study Design: Nonrandomized comparative

Device or Material: Polysorb suture ([PCL] Covidien) vs. V-Loc 180 barbed suture ([non-PCL] Covidien)

Contact Duration: 6 months

Dose: Size 0 braided PCL suture

Frequency/Duration: Single administration

Response: Vaginal cuff granulomatous

Patient characteristics (gender, mean age): 100% female. Polysorb (46.6±5.5years); V-Loc 180 (47.6±5.6years). Patients undergoing total laparoscopic hysterectomy.

Number per group: Polysorb (n=184); V-Loc 180 (n=306).

Observations on adverse effects: VCG occurred more often in the Polysorb group (8, 4.34%) compared to the V-Loc 180 group (6, 1.96%).

Timing of adverse effects: ≥6 months.

Factors that predict response: NR

3. Source Citation: Guastafierro et al. 2020[16]

Study Design: Nonrandomized comparative

Device or Material: Caprosyn suture ([PCL] Medtronic) vs. Steri-Strip ([non-PCL] 3M)

Contact Duration: 3 months

Dose: 4-0 PCL monofilament suture

Frequency/Duration: Single administration (continuous subcuticular closure) vs. 6 crisscrossed Steri-Strips

Response:
- Inflammation
- Pain

Patient characteristics (gender, mean age): 48 years, gender NR. Patients undergoing ECTR.

Number per group: Caprosyn (n=21); Steri-Strip (n=26).

Observations on adverse effects: Three suture patients (14.3%) reported inflammation; no inflammation reported in Steri-Strip group. There were no significant differences in the degree of pain for either group, with both groups reporting an immediate improvement in pain symptoms.

Timing of adverse effects: Sutures and Steri-Strips removed 10 days post-operative. Evaluations at 10 days and 1 month, with scar assessment at 3 months.

Factors that predict response: NR

cm: centimeter; ECTR: endoscopic carpal tunnel release; NR: not reported; PCL: polycaprolactone; RCT: randomized controlled trial; RR: relative risk; VCG: vaginal cuff granulomatous

Table 3: Packing - Health Effect (In Vivo) Human Studies

Local Response/Toxicity

1. Source Citation: Sari et al. 2021[19]

Study Design: RCT

Device or Material: Nasopore ([PCL] Stryker) vs. PRF ([non-PCL])

Contact Duration: 12 weeks

Dose: NR

Frequency/Duration: Single administration

Response:
- Crusting
- Granulation
- Stenosis

Patient characteristics (gender, mean age): Patients with bilateral CRS with nasal polyposis. 60% female, 41±8 years.

Number per group: 50. Nasal cavities randomized to treatment.

Observations on adverse effects:
Granulation – week 1: 36 patients (72%) had moderate granulation on the Nasopore side; 24 (36%) on the PRF side.
Granulation – week 3: 27 patients (54%) had no or mild granulation on the Nasopore side; 40 (80%) on the PRF side.
Granulation – week 4: 40 patients (80%) had no or mild granulation on the Nasopore side; 46 (92%) on the PRF side.
Crusting – week 1: 25 patients (50%) had moderate crusting on the Nasopore side; 14 (28%) on the PRF side.
Crusting – week 3: 27 patients (54%) had moderate and severe crusting on the Nasopore side; 13 (26%) on the PRF side.
Crusting or sinus ostium stenosis - Week 4: There were no statistically significant differences between the groups for crusting or frontal sinus ostium stenosis.
Frontal sinus ostium stenosis – week 12: No stenosis in 20 (40%) patients on the Nasopore side; 34 (68%) patients on the PRF side.

Timing of adverse effects: Followup at weeks 1, 3, and 4.

Factors that predict response: NR

2. Source Citation: Huang et al. 2020[20]

Study Design: RCT

Device or Material: Nasopore ([PCL] Stryker] vs. BISORB steroid-eluting stent ([non-PCL] Puyi Biotechnology)

Contact Duration: 30 days

Dose: NR

Frequency/Duration: Single administration

Response: No adverse events

Patient characteristics (gender, mean age): Patients with CRS and no nasal polyps; patients with CRS and nasal polyps who underwent ESS. 29.3% female, 42.4±12.5 years.

Number per group: 187; successful deployment in 181 sinuses. Nasal cavities randomized to treatment.

Observations on adverse effects: No complications occurred; no adverse events related to Nasopore occurred during the follow-up period. There were five and 21 adverse events that authors judged as having an indeterminate and unrelated relationship to the sinus stent and steroids (nasal pain, nose bleeding, headache, acute rhinosinusitis, etc.).

Timing of adverse effects: Not applicable.

Factors that predict response: Not applicable

3. Source Citation: Comer et al. 2019[21]

Study Design: RCT

Device or Material: Nasopore ([PCL] Stryker] or Nexfoam ([non-PCL] Hemostasis LLC) or Arista ([non-PCL] CR Bard) vs. no AHP

Contact Duration: 6 weeks

Dose: NR

Frequency/Duration: Single administration

Response:
- Edema
- Granulation
- Pain
- Obstruction

Patient characteristics (gender, mean age): Patients with bilateral CRS or RARS who were offered FESS. Overall: 42.4% male, 43 years; Nasopore: 54.0% female, 40.8 years; Nexfoam: 71.4% female, 46.4 years; Arista: 60% female, 47.8 years; Other: 33.3% female, 45.7 years.

Number per group: Overall n=59; Nasopore n=37; Nexfoam n=14; Arista n=5; Other n=3. Nasal cavity was randomized to AHP or no AHP.

Observations on adverse effects: Significant variance was identified in granulation at 1 week with highest scores associated with Nasopore use (P <0.01). Endoscopic outcomes were not found to differ significantly between AHP agents for edema or crusting at any time point.

Week 1: 6 patients with mild edema; 23 patients with mild granulation and 6 patients with moderate granulation.

Week 2: 22 patients with mild edema; 1 patient with mild granulation.

Week 6: 6 patients with mild edema; 0 patients with granulation.

Nasopore patients did not report crusting at any time point.

No difference in variance was noted for pain or obstruction at any time point.

Timing of adverse effects: Followup at weeks 1, 2, and 6.

Factors that predict response: NR

4. Source Citation: Burduk et al. 2017[22]

Study Design: RCT

Device or Material: Nasopore ([PCL] Polyganics) vs. impregnated gauze strip (non-PCL)

Contact Duration: 30 days

Dose: 4 cm Nasopore. 4 cm gauze strip with 2g Oxycort ointment (Jelfa)

Frequency/Duration: Single administration

Response:
- Blockage
- Headache
- Pain
- Pressure

Patient characteristics (gender, mean age): Patients with CRS, with and without nasal polyps, undergoing bilateral ESS. 44% female, 47.5±9.8 years.

Number per group: 50 individuals with nasal cavities randomized to treatment.

Observations on adverse effects: A significant difference in pressure was found between the Nasopore and control sides on day 10 ($p<0.04$) with patients reporting lower feeling of nose pressure on the Nasopore side. No differences were observed on the 2nd and 30th days post-operatively. Nasopore had lower scores with respect to nose blockage on the 2nd ($P<0.04$) and 10th ($p<0.02$) days, but no significant difference by the 30th day. Slightly (non-significant) lower scores for headache and nasal pain were recorded for the Nasopore group during follow-up visits.

Timing of adverse effects: Highest VAS scores recorded at 2 days, then 10 days. Subjective scores for Nasopore negligible at day 30.

Factors that predict response: NR

5. Source Citation: Jung et al. 2017[23]

Study Design: RCT

Device or Material: Nasopore ([PCL] Polyganics) vs Tisseel fibrin sealant ([non-PCL] Baxter)

Contact Duration: 12 weeks

Dose: 4 cm Nasopore; 0.6 to 1.0 mL Tisseel

Frequency/Duration: Single administration

Response:
- Crusting
- Granulation
- Obstruction
- Pain during packing
- Pain on dressing
- Pressure
- Stenosis

Patient characteristics (gender, mean age): Patients with CRS, with and without nasal polyps, undergoing bilateral FESS. 40% female, 37.5 years.

Number per group: 35. Nasal cavity randomized to treatment.

Observations on adverse effects: The mean score for crusting at 1 and 2 weeks was significantly higher in the Nasopore side ($p<0.05$). The Nasopore side also had more severe granulation formation at 1 month ($p<0.03$). There was no significant difference between sides in terms of mean scores for frontal sinus ostium stenosis throughout follow-up There was no significant difference between sides in terms of subjective symptoms (pain during packing, pain during dressing, facial pressure), except for obstruction, which had a higher rating on the Nasopore side ($p<0.05$) with a score of 5.2/10 versus 3.5. No other complications were identified during post-op follow-up.

Timing of adverse effects: Crusting 1-2 weeks; granulation at 1 month.

Factors that predict response: NR

6. Source Citation: Raghunandhan et al. 2014[24]

Study Design: RCT

Device or Material: Nasopore ([PCL] Polyganics) vs. Merocel ([non-PCL] Medtronic)

Contact Duration: 2 weeks

Dose: 4 cm Nasopore; 4 cm Merocel

Frequency/Duration: Single or multiple administration

Response:
- Migration
- Obstruction
- Pressure

Patient characteristics (gender, mean age): Patients with CRS undergoing bilateral FESS. 33.3% female, 21 to 63 years.

Number per group: 30. Nasal cavity randomized to treatment.

Observations on adverse effects: Two patients (6.6%) developed bleeding due to posterior migration of the Nasopore material requiring packing of additional Nasopore. No allergic reactions to either of the materials or any foreign body reaction with granulation formation at the site. Mean score for obstruction (7.2/10 for Nasopore and 7.6 for Merocel) and pain pressure due to nasal packing (4.6/10 for Nasopore and 5.4 for Merocel) symptoms on the day of surgery was comparable.

Timing of adverse effects: Day of surgery.

Factors that predict response: NR

7. Source Citation: Zhao et al. 2013[17]

Study Design: Systematic review

Device or Material: Nasopore ([PCL] Stryker) vs. Merocel ([non-PCL] Medtronic)

Contact Duration: NR

Dose: NR

Frequency/Duration: Single administration

Response: Pain

Patient characteristics (gender, mean age): Patients receiving absorbable or nonabsorbable middle meatus spacers after ESS. Gender and age NR.

Number per group: Two of 11 studies involved Nasopore. N=19 and 37. Nasal cavities randomized to treatment.

Observations on adverse effects: One of 2 relevant studies reporting on a non-efficacy outcome of interest (pain). No significant difference in mean pain scores between Nasopore (3.33/10) and Merocel (3.7/10) at 1 week following surgery (MD -0.37; 95% CI, -1.76 to 1.02). There was a non-significant trend for reduced pain with Merocel.

Timing of adverse effects: 1 week.

Factors that predict response: NR

8. Source Citation: Wang et al. 2014[18]

Study Design: Systematic review

Device or Material: Nasopore ([PCL] Polyganics) vs. Merocel ([non-PCL] Medtronic)

Contact Duration: NR

Dose: NR

Frequency/Duration: Single administration

Response:
- Bleeding upon removal
- Obstruction
- Pain in situ
- Pain upon removal
- Pressure

Patient characteristics (gender, mean age): Patients undergoing post-op of nose including FES, septoplasty, conchotomy, or a combination. Gender NR, age range 5 to 76 years.

Number per group: N = 30 to 160. 7 RCTs included. Nasal cavity randomized to treatment.

Observations on adverse effects:
Pain in situ (5 studies, 213 per arm): Pain score in the Nasopore group was lower than the Merocel group (SMD, -0.68; 95% CI, -1.16 to -0.20; p=0.005).
Pain upon removal (6 studies, 251 per arm): Nasopore significantly reduced pain upon removal compared with Merocel. (SMD, -1.62; 05% CI, -2.35 to -0.71; p=0.005).
Bleeding upon removal (6 studies, 318 per arm): The Nasopore group received significantly better control of bleeding upon removal than the Merocel group (SMD, -0.99; 95% CI, -1.65 to -0.34; p=0.003).
Obstruction (4 studies, 167 per arm): No significant difference was observed in nasal obstruction during packing between the two groups (MD, 0.03; 95% CI, -1.02 to 1.08; p=0.96).
Pressure (4 studies, 167 per arm): There was significantly less nasal cavity pressure in the Nasopore group (MD, -0.79; 95% CI, -1.49 to -0.09; p=0.03).

Timing of adverse effects: NR

Factors that predict response: NR

9. Source Citation: Piski et al. 2017[25]

Study Design: RCT

Device or Material: Nasopore ([PCL] Polyganics) vs. no packing

Contact Duration: 12 weeks

Dose: 4 cm Nasopore

Frequency/Duration: Single administration

Response:
- Crusting
- Edema

Patient characteristics (gender, mean age): Patients with CRS undergoing bilateral ESS. 46.7% female, 58.87 years (range 33-75).

Number per group: 30. Nasal cavities randomized to treatment.

Observations on adverse effects: 4 weeks: Crust formation occurred in a higher number of patients on the Nasopore-packed side, but the degree of crust build-up was greater on the unpacked side. Scores for edema were almost equal in both nasal fossae.

12 weeks: all clinical signs showed better results on the Nasopore-packed side, though differences were not statistically significant.

Timing of adverse effects: Crusting and edema at 4 weeks.

Factors that predict response: NR

AHP: absorbable hemostatic packing; cm: centimeter; CRS: chronic rhinosinusitis; ESS: endoscopic sinus surgery; FESS: functional endoscopic sinus surgery; g: gram; NR: not reported; PCL: polycaprolactone; RCT: randomized controlled trial; PRF: platelet-rich fibrin; RARS: recurrent acute rhinosinusitis

Table 4: Dressing - Health Effect (In Vivo) Human Studies

Local Response/Toxicity

1. Source Citation: Rahimi et al. 2020[26]

Study Design: Systematic review

Device or Material: Suprathel, Oasis (Smith & Nephew), Biatain-Ibu (Coloplast), Mepitel (Mölnlycke), Biobrane (Smith & Nephew), Jelonet (Smith & Nephew), Omiderm (Dr Spiller), Xenoderm (Medical Biomaterial Products), autologous graft, allogenic graft, amnion, paraffin gauze, polyhexanide gel

Contact Duration: NR

Dose: NR

Frequency/Duration: NR

Response:
- Detachment
- Inferior maximal extension, elasticity, retraction, and pliability

Patient characteristics (gender, mean age):
Glik et al 2017: 100% males with 100% thermal burns. Mean age 49 years.
Rashaan et al. 2016: 52% females, aged 5 months to 14 years.
Pfurtscheller et al. 2014: 100% female (1 patient). 10 y/o.
Highton et al. 2013: 61% females. Age range 5 months to 11 years.
Keck et al. 2012: gender NR, median 45 years (range 25 to 83).
Madry et al. 2011: 76% male, age NR.
Schwarze et al. 2008: gender NR, mean age 40.4 years.
Schwarze et al. 2007: gender NR, mean age 39.6 years.
Gender and age NR for 4 studies (Everett et al. 2017, Rahmanian-Schwarz et al. 2011, Markl et al. 2010, and Uhlig et al. 2007).

Number per group: 14 included studies. Total N = 331 (n for Suprathel not available in most studies).

Observations on adverse effects: Due to the limited information available in the review, we pursued information on the individual studies. No abstracts were available for 2 case reports (Fischer et al. 2016, Lindford 2011). Full text was available for 1 single arm study (Rashaan 2016) and abstracts for 11 studies.

3 RCTs
Markl et al. 2010: 77 patients being treated for split-thickness skin graft donor sites with Suprathel, Biatain-Ibu, and Mepitel. Safety NR although no difference in healing time was reported.

Schwarze et al. 2008: 30 patients with second-degree burn injuries partly treated with Suprathel or Omiderm dressing. Suprathel showed better attachment and adherence to wounds. No AEs reported.

Schwarze et al. 2007: 22 burn patients partly treated with Suprathel or Jelonet. Suprathel showed excellent plasticity with attachment and adherence to wound surfaces.

4 nonrandomized comparative studies
Glik et al. 2017: 30 patients, Suprathel synthetic dressing (n=24) vs. Oasis porcine-derived wound dressing (n=6). Authors noted no inflammatory reaction up to 3 weeks with either dressing.

Keck et al. 2012: 18 patients, Suprathel vs. split-thickness skin graft (STSG) for deep-partial-thickness burns. Followup to 90 days. No AEs reported.

Rahmanian-Schwarz et al. 2011: 34 patients with acute burns treated with Suprathel or Biobrane. Skin elasticity was measured at 8 months. Results indicated the Biobrane group demonstrated superior Cutometer® parameters in

regards to maximal extension, elasticity, retraction, and pliability. No significant differences however were reported for viscoelastic analysis.

Uhlig et al. 2007: 22 patients with second-degree burns treated with Suprathel or Omiderm dressings. No allergic reactions were reported. The ability of the material to resorb ensured pain-free removal after complete healing of the wound.

4 single arm studies
Everett et al. 2017: 17 patients with superficial and partial-thickness burns. Authors noted that the staff found the self-adherence and elasticity of the dressing made it easy to apply to and stay adherent, especially in areas of difficult contour.

Highton et al. 2012: 33 children with partial thickness burns receiving Suprathel. Hypertrophic scarring was reported although significantly associated with infection.

Madry et al. 2011: 21 patients with wound burns, frostbite, and Lyell's syndrome. Safety NR.

Rashaan et al. 2016: 21 children with partial thickness burns receiving Suprathel. At 3-5 days post-Suprathel application (first outer layer dressing change), Suprathel was completely detached in 9 (43%) patients. Authors noted this may be due to lack of debridement with VersaJet hydrosurgery since no detachment was seen in this group.

1 case report
Pfurtscheller et al. 2014. Burn-like wounds. No AEs reported.

Timing of adverse effects: Detachment noted at 3-5 days. Inflammation measured at 3 weeks. Cutometer parameters measured at 8 months.

Factors that predict response: NR

2. Source Citation: Hakkarainen et al. 2016[27]

Study Design: Nonrandomized comparative (within-subject)

Device or Material: Suprathel, nanofibrillar cellulose (NFC)

Contact Duration: Suprathel, 21.6 days; NFC, 17.8 days (mean interval from application to self-detachment)

Dose: Suprathel, 583 cm2; NFC, 920 cm2 (mean surface area of skin graft donor site covered)

Frequency/Duration: Single application

Response: Skin graft donor site irritation (skin tears, inflammation)

Patient characteristics (gender, mean age): 4 males, 1 female. Mean age 56.2 years.

Number per group: 5 (each patient received both materials).

Observations on adverse effects: 2 of 5 patients experienced some irritation in skin graft donor sites after Suprathel was removed (skin tears in 1 patient, inflammation in 1 patient).

Timing of adverse effects: Skin tear: upon removal (postoperative day 28). Inflammation: a few days after removal (approximately postoperative day 24).

Factors that predict response: NR

AE: adverse events; NR: not reported; RCT: randomized controlled trial

Table 5: Orthopedic Implant - Health Effect (In Vivo) Human Studies

Local Response/Toxicity

1. Source Citation: Smeraglia et al. 2018[28]

Study Design: Systematic review

Device or Material: Artelon CMC Spacer ([PCL] Artimplant)

Contact Duration: Longest followup (months): 26, 33, 63 of studies reporting

Dose: NR

Frequency/Duration: Single administration

Response:
- Foreign body reaction
- Pain
- Swelling
- Synovitis

Patient characteristics (gender, mean age): Patients with basal thumb joint OA. 76% female, 57.3 years.

Number per group: n = 3 to 29 for 4 single arm studies reporting complications. Total N=47.

Observations on adverse effects:
Robinson and Muir 2011 (case series, n=3): Histological analysis of the explanted Artelon material showed a large number of foreign body-type giant cells within the soft tissue and bone closely associated with the implant.
Clarke et al. 2011 (case series, n=29): 12 patients (41%) displayed post-operative complications including swelling (3, 10%), synovitis (1, 3%), and persistent pain (7, 24%).
Park et al. 2012 (case series, n=9): No complications occurred in Artelon group including no evidence of foreign body reaction. One patient reported synovitis after receiving corticosteroid injection.
Richard et al 2014 (case series, n=6): Non-specified complications in 4 of 6 thumbs treated, with 3 thumbs requiring secondary procedure. Foreign body reaction noted in 2 of 6 thumbs.

Timing of adverse effects:
Robinson and Muir 2011: NR.
Clarke et al. 2011: 8 month follow-up (1 to 26 months).
Park et al. 2012: 23.4 month follow up (13 to 33 months).
Richard et al. 2014: 39.3 month follow-up (6 to 63 months).

Factors that predict response: NR

2. Source Citation: Wajon et al. 2015[29]

Study Design: Systematic review

Device or Material: Artelon CMC Spacer ([PCL] Artimplant) vs. traditional trapeziectomy with IA

Contact Duration: 1 year

Dose: NR

Frequency/Duration: Single administration

Response:
- Swelling
- Pain

Patient characteristics (gender, mean age): Patients with basal thumb joint OA. 61 females, 9 males received Artelon. 59 years.

Number per group: n=113 over two relevant joint resurfacing studies; only 1 RCT (Nilsson 2010, n=98; 63 Artelon, 35 surgery in analysis) reported AEs.

Observations on adverse effects: Mild to moderate swelling (RR=0.09, 95% CI: 0.01 to 0.61): Artelon (21, 33%), trapeziectomy with IA (1, 3%). Reoperation due to pain (RR=0.14, 95% CI: 0.01 to 2.36): Artelon (6, 9.5%), trapeziectomy with IA (0%). Authors are uncertain of the benefits either technique has with regards to pain, adverse events, or treatment failure over the other.

Timing of adverse effects: 1 year

Factors that predict response: NR

3. Source Citation: Blount et al. 2013[30]

Study Design: Nonrandomized comparative

Device or Material: Artelon Spacer ([PCL] Small Bone Innovations) vs. traditional trapeziectomy with LRTI

Contact Duration: 30 months

Dose: NR

Frequency/Duration: Single administration

Response:
- Instability
- Inflammatory reaction

Patient characteristics (gender, mean age): Patients with carpometacarpal arthritis. Patient gender and mean age NR.

Number per group: Artelon (38 enrolled, 32 analyzed); LRTI (n=10 patients receiving 13 LRTI procedures).

Observations on adverse effects: Instability: Artelon - problems with early instability led to an increase in splinting from 2-3 weeks to 5-6 weeks. 12 of 32 Artelon patients (37%) required revision surgery with removal of implant and salvage arthroplasty due to recurrent arthritis symptoms or inflammatory reaction, compared to 0% revision rate in LRTI group.

Timing of adverse effects: Average follow-up was 30 months for the Artelon group and 48 months for the LRTI group.

Factors that predict response: NR

IA: interpositional arthroplasty; LRTI: ligament reconstruction and tendon interposition; NR: not reported; OA: osteoarthritis; PCL: polycaprolactone; RR: relative risk

Table 6: Dermal Filler - Health Effect (In Vivo) Human Studies

Local Response/Toxicity

1. Source Citation: Lin and Christen 2020[31]

Study Design: Single arm

Device or Material: Bioresorbable PCL-based filler (Ellansé®; Sinclair Pharmaceuticals)

Contact Duration: Up to 3 years

Dose: Average 5.04 mL, 1 mL per syringe

Frequency/Duration: Most patients: single treatment; 127 patients: multiple treatments

Response:
- Bruising/hematoma
- Discoloration at injection site
- Malar edema
- Palpable lumps
- Swelling/edema

Patient characteristics (gender, mean age): NR

Number per group: 780 total (1111 treatments in the subcutaneous or supraperiosteal level of the facial areas).

Observations on adverse effects: 50 cases (4.5%) of swelling/edema that lasted longer than 2 weeks (prolonged swelling), 30 cases (2.7%) of bruising, 8 cases (0.72%) of malar edema (late-onset edema of the mid-face), 5 cases

(0.45%) of temporarily palpable lumps and 2 cases (0.18%) of discoloration at injection site due to placement too superficially. Authors noted that edema lasting longer than 2 weeks was associated with higher-volume injection (8.36 mL per treatment).

Timing of adverse effects:
Within 2 weeks post-treatment: bruising/hematoma, swelling/edema (duration >2 weeks), temporary palpable but nonvisible lumps.
>2 weeks to 3 years post-treatment: malar edema
10 months and 11 months post-treatment: discoloration.

Factors that predict response: NR

2. Source Citation: Kim J 2019[32]

Study Design: Single arm

Device or Material: M-version PCL-based filler (Ellansé-M [PCL-2], Sinclair Pharmaceuticals)

Contact Duration: 1 year (10 patients); 4 years (3 patients)

Dose: 3 cc of diluted PCL (0.5 cc) filler; 0.0005 cc per site using an injector

Frequency/Duration: Single administration

Response:
- Ecchymosis
- Inflammatory response including FBGCs, macrophages, monocytes, and eosinophils
- Mild swelling
- Prolonged swelling

Patient characteristics (gender, mean age): 100% female, mean age 38.7 years (range, 28 to 68).

Number per group: 13 patients treated for thin skin with skin atrophy due to aging and moderate-to-severe levels (Class II and III in Fitzpatrick's Classification) of facial wrinkles.

Observations on adverse effects: All patients experienced mild swelling for 1 or 2 days, but no cases with prolonged swelling lasted more than 5 days. Seven patients (53.8%) experienced ecchymosis on injection sites (especially on thinner skin areas). This occurred for 2 or 5 days due to the injector using multiple sharp needles on 1000 sites.

Histology results indicated:

At 2 weeks post-treatment, the inflammatory response included numerous macrophages and FBGCs around the PCL particles; no eosinophils were detected.

At 1 year post-treatment, numerous FBGCs, macrophages and monocytes were detected all around the PCL particles. 5 eosinophils were detected in 10 specimen slides.

At 1 and 4 years, all PCL particles were surrounded by an FBGC. At 4 years, 3 eosinophils were found in 10 slides.

At 2 weeks and 1 year, the PCL particle was approximately 40 microns, smooth on the surface, and sphere-shaped. At 4 years, the filler particles decreased, were irregular with rough surfaces, and almost all cleaved (split).

There were no serious adverse events (e.g., granuloma, embolism, skin necrosis, skin irregularities, nodules, dermal lumps, or prolonged pain).

Timing of adverse effects: Mild swelling: 1 to 2 days; Prolonged swelling: 5 days or less; Ecchymosis: 2 or 5 days. At 2 weeks, the inflammatory response included FBGCs and macrophages. At 1 year, the inflammatory response also included eosinophils and monocytes. At 4 years, FBGCs and eosinophils were still detected.

Factors that predict response: NR

3. Source Citation: Bae et al. 2016[33]

Study Design: Single arm

Device or Material: Ellansé-M

Contact Duration: 24 months

Dose: 1.1 mL

Frequency/Duration: Single administration

Response:
- Ecchymosis
- Edema

Patient characteristics (gender, mean age): 98% women (n=57); 2% men (n=1). Aged 20 to 65 years.

Number per group: 58 patients with uneven contour (n = 29, 50%), or a concavity due to a prominent brow ridge and relative frontal bone bossing, a flat surface, or seeking volume augmentation (n = 29, 50%). All patients received an injection of botulinum toxin 2 weeks before PCL forehead augmentation.

Observations on adverse effects: Injection-related adverse events included edema and ecchymosis (data not shown). Events resolved without interventions. No lumpiness or uneven contours were detected. No serious adverse events (e.g., vascular accidents) were reported.

Timing of adverse effects: NR

Factors that predict response: NR

cc: cubic centimeter; FBGC: foreign body giant cell; HCl: hydrochloride; mL: milliliter; NR: not reported; PCL: polycaprolactone

Table 7: Meniscus Scaffold - Health Effect (In Vivo) Human Studies

Local Response/Toxicity

1. Source Citation: Ranmuthu et al. 2019[34]

Study Design: Systematic review

Device or Material: Actifit ([PCL] Orteq) alone, and Actifit vs. CMI ([non-PCL] Ivy Sports Medicine)

Contact Duration: 24 to 72 months

Dose: NR

Frequency/Duration: Medial, lateral, and bilateral administration

Response:
- Complications (non-specified)
- Degradation and irregular margins
- Failure
- Stiffness
- Synovitis

Patient characteristics (gender, mean age): 10.5% to 46.7% female, 30.0 to 34.4 years.

Number per group: 15 to 44. 5 relevant studies (4 single arm, 1 nonrandomized comparative study). 121 patients received Actifit.

Observations on adverse effects:
Actifit vs. CMI: joint stiffness (1 (4%)), synovitis (4 (16%)) with Actifit. Persistent synovitis in 1 (3.5%) patient with CMI. No signs of necrosis in either group.

Actifit (4 single arm): One study reported knee stiffness in 1 patient (5.3%) receiving ACL reconstruction plus scaffold implantation. One study reported 3 complications (non-specified). One study reported no complications. One study did not report complications.

3 of 5 studies indicated that the Actifit scaffold tended to form irregular margins and reduce in size over time after 24 months (2 studies) and after 60 months (1 study). Actifit failure rates ranged from 5.3% to 31.8%.

Timing of adverse effects: 24 to 72 months.

Factors that predict response: Higher rate of failure for patients with a lateral compartment defect possibly due to difficulty in scaffold application in lateral meniscus, which bears more load than medial meniscus.

2. Source Citation: Houck et al. 2018[35]

Study Design: Systematic review

Device or Material: Actifit ([PCL] Orteq) alone, and Actifit vs. CMI ([non-PCL] Ivy Sports Medicine)

Contact Duration: mean 45 months

Dose: NR

Frequency/Duration: Single administration per knee

Response:
- Failure (reoperation due to pain)
- Meniscal extrusion

Patient characteristics (gender, mean age): Total over 19 studies: 24% female, 36 years.

Number per group: Total over 19 studies (17 (89%) single arm studies): Actifit (n=347); CMI (n=311). 12 single arm studies evaluated Actifit (n=347), 7 studies evaluated CMI (n=311).

Observations on adverse effects: Treatment failure occurred in 9.9% of Actifit patients and 6.7% of CMI patients. Failure definitions varied among studies, but was largely the need for reoperation due to pain in the Actifit group.

MRI demonstrated that Actifit implantation was followed by an increase of coronal meniscal extrusion particularly when implanted into the medial compartment. Otherwise, MRI demonstrated minimal joint space narrowing, moderately stable cartilage, and no significant chondral damage.

Timing of adverse effects: Actifit failure at mean 40 months. CMI failure at mean 44 months.

Factors that predict response: Significantly higher failure occurrence on the lateral compartment.

3. Source Citation: Papalia et al. 2013[36]

Study Design: Systematic review

Device or Material: Actifit ([PCL] Orteq) alone, and Actifit vs. CMI ([non-PCL] Ivy Sports Medicine)

Contact Duration: mean 12 months to 24 months

Dose: NR

Frequency/Duration: Single administration per knee

Response:
- Dislocation of scaffold
- Failure (reoperation)
- Non-integrated scaffold
- Pain
- Tear in scaffold

Patient characteristics (gender, mean age): Total over 15 studies: 17.3% female, 36.9 years (16 to 67).

Number per group: Actifit only used in 3 studies (2 single arm (n=62), 1 nonrandomized comparative (n=23, 11 Actifit, 12 CMI). Overall, 73 patients received Actifit.

Observations on adverse effects: Verdonk et al. (n=52): pain (5.8%), non-integrated scaffold (3.8%), tear in scaffold (1.9%), dislocation of scaffold (1.9%), and failure leading to eventual unicompartmental knee arthroplasty

(1.9%). Authors noted that a rate of implant failure doubled on the patients with lateral meniscal injury when compared with those receiving surgery on the medial side (three versus six failures out of nine total reoperations). The failures on the medial side were all related to the procedure, whereas five of six reoperations on the lateral meniscus were considered to have a possible or definite relationship with the scaffold.

Timing of adverse effects: Verdonk et al. mean follow-up at 2 years.

Factors that predict response: NR

ACL: anterior cruciate ligament; CMI: collagen meniscus implant; NR: not reported: PCL: polycaprolactone

Table 8: Drug-eluting stents - Health Effect (In Vivo) Human Studies

Local Response/Toxicity

1. Source Citation: Wu et al. 2019[39]

Study Design: RCT and registry

Device or Material: RCT: Xinsorb BRS (bio-resorbable scaffold) (Huaan Bio-technology), Tivoli (Essen Technology) (non-PCL) Registry: Xinsorb BRS

Contact Duration: 12 months

Dose: NR

Frequency/Duration: Single administration

Response:
- Target lesion revascularization (TLR)
- Target vessel (TV)-related myocardial infarction (MI)
- Target lesion failure (TLF; cardiac death, TV-related MI, or ischemia-driven TLR)

Patient characteristics (gender, mean age): NR

Number per group: RCT: Xinsorb BRS (n = 200), Tivoli (n = 195). Registry: Xinsorb BRS (n = 798).

Observations on adverse effects:
RCT:
In-device restenosis: 0% (both groups).
TLR: 2.0% (Xinsorb), 5.1% (Tivoli); p = ns.
TV-related MI: 0.5% (Xinsorb), 0% (Tivoli).
TLF: 2.5% (Xinsorb), 5.1% (Tivoli); p = ns.
Registry:
TLR: 0.9%.
TV-related MI: 0%.
TLF: 0.4%.

Timing of adverse effects: NR

Factors that predict response: NR

2. Source Citation: Saito et al. 2014[37]

Study Design: RCT (CENTURY II trial)

Device or Material: Ultimaster (Terumo), Xience (Abbott Vascular) (non-PCL)

Contact Duration: 3-4 months

Dose: NR

Frequency/Duration: Single administration

Response:

- Clinically indicated TLR
- Restenosis
- TV-related myocardial infarction (MI)
- TLF (cardiac death, TV-related MI, or clinically indicated TLR)

Patient characteristics (gender, mean age): 20% female; mean age 65 years.

Number per group: Ultimaster (n = 551 per-protocol); Xience (n = 550 per-protocol). Restenosis was assessed in a subsample of patients who received angiograms at follow-up (214 Ultimaster, 215 Xience). Results were reported on the per-protocol population. ITT population was 562 Ultimaster, 557 Xience.

Observations on adverse effects:
Clinically indicated TLR: 2.18% Ultimaster, 1.64% Xience; p = ns.
In-stent restenosis: 1.27% Ultimaster, 1.21% Xience; p = ns.
In-segment restenosis: 3.80% Ultimaster, 2.83% Xience; p = ns.
TV-related MI: 1.27% Ultimaster, 2.18% Xience; p = ns.
TLF: 4.36% Ultimaster, 4.91% Xience; p = ns.

Timing of adverse effects: NR

Factors that predict response: NR

3. Source Citation: Lemos et al. 2012[38]

Study Design: RCT (PAINT trial)

Device or Material: Infinnium, Supralimus, Milennium Matrix (non-PCL); all manufactured by Sahajanand Medical Technologies

Contact Duration: 12 months

Dose: NR

Frequency/Duration: Single administration

Response:
- Cardiac death or nonfatal MI
- TLR
- Major adverse cardiac events (cardiac death, MI, or target vessel revascularization)

Patient characteristics (gender, mean age): Percent male: 64.1% (PCL stents), 66.7% (non-PCL). Mean age: 59.9 years (PCL stents), 58.5 (non-PCL).

Number per group: Infinnium (n = 111), Supralimus (n = 106), Milennium Matrix (n = 57).

Observations on adverse effects: Cardiac death or nonfatal MI: 9.0% PCL stents, 7.1% non-PCL; p = ns. TLR: 8.2% PCL stents, 28.2% non-PCL; p <0.01. Major adverse cardiac events: 14.6% PCL stents, 33.3% non-PCL; p <0.01.

Timing of adverse effects: NR

Factors that predict response: NR

4. Source Citation: Yasumura et al. 2021[40]

Study Design: Nonrandomized comparative

Device or Material: Ultimaster, Synergy (Boston Scientifics Corp.) (non-PCL), Xience (non-PCL)

Contact Duration: 20 months

Dose: NR

Frequency/Duration: Single administration

Response: Major adverse cardiac events (cardiac death, MI, or target vessel revascularization)

Patient characteristics (gender, mean age): Percent male: 88% (Ultimaster), 100% (Synergy), 81% (Xience). Mean age: 67.6 years (Ultimaster), 69.9 years (Synergy), 64.1 years (Xience).

Number per group: Ultimaster (n = 26), Synergy (n = 30), Xience (n = 21).

Observations on adverse effects: Among patients who received Ultimaster, 2 (8%) experienced major adverse cardiac events (TVR for in-stent restenosis in both cases); no major adverse cardiac events occurred in the other two groups.

Timing of adverse effects: NR

Factors that predict response: NR

NR: not reported; NS: not significant; PCL: polycaprolactone; RCT: randomized controlled trial;

Appendix E. References

References

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Appendix F. Surveillance Event Reports - PSO and Accident Investigation

Provided with this report as separate Excel spreadsheet.

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Appendix G. Regulatory and Manufacturer Safety Alerts

Specific search terms are provided here. The associated alerts are provided with this report as a separate PDF.

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