MEDICAL DEVICE MATERIAL PERFORMANCE STUDY

Polyethylene glycol Safety Profile

Report Details

Date of Submission

September 8, 2021

Prepared For

U.S. FDA Center for Devices and Radiological Health

Submitted to

Ed Margerrison, PhD

Director, Office of Science and Engineering Laboratories (OSEL)
Center for Devices and Radiological Health
U.S. Food and Drug Administration

ECRI Corporate Governance

Michael Argentieri, MS
Vice President, Technology and Safety
Phone: (610) 316-2766
Email: margentieri@ECRI.org

Dheerendra Kommala, MD
Chief Medical Officer, Executive Committee
Phone: (610) 825-6000 ext. 5090
Email: dkommala@ECRI.org

Project Manager

Christopher N. Schabowsky, PhD, CCE
Director, Accident and Forensic Investigations
Phone: (540) 272-2740
Email: cschabowsky@ECRI.org

If you have any questions or require additional information, please do not hesitate to call the Project Manager.

ECRI The Most Trusted Voice in Healthcare

Table of Contents

Table of Tables

Executive Summary

Key Points

1. Searches identified 1245 citations; 41 articles were selected for inclusion.

2. The local responses reported in the largest number of studies were bleeding and hematoma, and they were associated with moderate to very low quality of evidence. Local responses for polyethylene glycol (PEG) as a material, aneurysm sealant, mesh, embolic agent, wound dressing, bone filler/grafting, dermal filler (no evidence), hydrogel tissue marker (no evidence), and eye surgery dye were associated with very low quality of evidence.

3. Evidence for systemic responses was reported for sealants, aneurysm sealant, adhesion barrier, embolic agent, and hydrogel spacer although the direct association with PEG is uncertain in most cases. In 2 studies, systemic responses from a PEG embolic agent (LifePearl microspheres) and a hydrogel spacer (SpaceOAR) were attributed to the device. The quality of evidence for systemic responses was rated low to very low.

4. ECRI PSO identified 66 reports that involved complications. The top 5 complications included: 1) Hemorrhage/Hematoma - 25 (37.9%), 2) Device malfunction/failure - 19 (28.8%), 3) Durotomy - 10 (15.2%), 4) CSF leak 4 (6.1%), and 5) Expired – 2 (3.0%). 18 reports resulted in harm to the patient. Nearly 70% of the PSO reports were associated with vascular closure devices including all reports of hemorrhage and 90% of device malfunction/failure

5. Two PRN reports detail that after deployment the vascular access closure devices balloons deflated and ruptured causing the vascular closure to fail.

6. Evidence gaps:

    a. Long-term human randomized controlled trial (RCTs) for all PEG device categories. Of the 12 device categories, only 1 (8%) category included more than 2 RCTs. In addition, follow-up for some categories (e.g., sealants) was limited to 12 weeks.
    b. Long-term RCTs for PEG as a material. Only 2 animal studies were identified in this category, and while both were controlled studies, only 50 animals were evaluated up to 16 weeks.
    c. Additional research on systemic responses, including patient or material factors, for all PEG device categories. Systemic responses were only investigated in 12 (29%) studies, with no studies investigating PEG for vascular closure, mesh, wound dressing, bone filler/grafting, dermal filler, hydrogel tissue marker, and eye surgery dye. Studies should measure complications from a prostate-rectal spacer (SpaceOAR) prior to radiation so a more direct association could be ascertained, although the responses may still be due to the disease process or patient comorbidities.
    d. No evidence was available for 1 device each in 2 categories (REMAKE for dermal filler, TraceIT for hydrogel tissue marker). Of the 10 remaining device categories, evidence was not available for 34 devices of interest; including 8 (88%) bone filler/grafts and 5 (83%) wound dressings. Of the overall evidence base, limitations included small enrollment, lack of reporting patient characteristics (e.g., age, gender) and study characteristics (e.g., administered dose), general focus on middle-aged patients, and limited focus on anatomies examined (e.g., maxilla for bone fillers).

Overview - Polyethylene glycol (PEG)

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 Polyethylene glycol. 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 and between human and animal studies (see specific responses/events under 1a. below). The majority of ECRI surveillance data were related to device malfunction or failure; however, it was unclear in the data if this was related to material response due to insufficient biocompatibility or mechanical integrity and use of the device.

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

i. 1 animal study evaluating PEG as a material within ridge defects after molar removal in dogs reported marked hemorrhage and membrane detachment in 28.5% of animals. 1 animal study addressing use of 5% PEG 4000 with polypropylene mesh to repair abdominal wall defects in rats reported normal lymphohistiocytic infiltration.
ii. 9 studies examining sealants reported varying local responses when PEG was used for closure in ocular, pleural, vascular, gynecological, spinal/cranial, and rectal anatomies. Higher incidence of complications were reported for pleural (40.5% rate for pneumothorax) and rectal closures (37.4% acute Grade 1 toxicities), while lower incidence of complications were reported for vascular (0.9% pericardial effusion), gynecological (2.9% abdominal pain), and spinal/cranial closures (0.8% hematoma).
iii. Studies examining endovascular aneurysm sealing (EVAS) with Nellix commonly reported endoleak and device migration. Hematoma, pseudoaneurysm, and thrombosis were reported less frequently.
iv. 1 of 4 studies addressing adhesion barriers reported that serious adverse events (SAEs, not defined) were limited in studies focused on gynecological and colorectal surgeries.
v. Studies of vascular closure rarely reported pain, while bleeding and hematoma were commonly reported.
vi. Seroma and pain were common local responses from PEG mesh used in inguinal and ventral hernia repair. Hematoma however only occurred with inguinal hernia repair, while hernia recurrence and mesh protrusion only occurred with ventral hernia repair.
vii. Embolic agent-related responses to LifePearl microspheres in patients with hepatocellular carcinoma included bile duct dilations (n=8), bilomas (n=7), and portal vein thromboses (n=4). False aneurysm of segment V in the liver, and chronic artery occlusion and stenosis of coronary ostium artery occurred in 1 patient each.
viii. Epidural hematoma and pseudomeningocele occurred after applying Hemopatch wound dressings post-cranial and intradural spinal procedures, while seroma occurred post- thyroidectomy.
ix. Dehiscence was reported from MembraGel bone graft used in the posterior maxilla or mandible.
x. Local responses measured prior to radiation therapy in prostate cancer patients receiving a hydrogel spacer (SpaceOAR) included perineal abscess requiring drainage and rectourethral fistula requiring colostomy in 3 patients each. Purulent draining from perineum, perirectal fistula, proctitis, rectal ulcer and hemorrhage occurred in 1 patient each.
xi. No complications were reported up to 12 months after use of eye surgery dyes (ILM-Blue™ and MembraneBlue-Dual™).
xii. The overall quality of evidence related to local host responses was moderate to very low, with variation across different device categories.
xiii. Very little evidence (≤4 studies) was included regarding local host responses for PEG as a material, aneurysm sealant, adhesion barrier, mesh, embolic agent, wound dressing, bone filler/grafting, and eye surgery dye.

xiv. No evidence was included regarding local host responses for dermal fillers or hydrogel tissue marker.

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

i. Two animal studies examining PEG as a material detected hemorrhage, inflammatory reaction (containing lymphocytes and macrophages), and membrane detachment postoperatively; and fibrosis up to 21 days. Local host responses for sealants were noted within 90 minutes postoperative (foreign body sensation [ocular]), 8 days and 111 days (pseudomeningocele [spinal/cranial]), and within 30 days (bronchopleural fistula [pleural]). EVAS with Nellix resulted in endoleak within 30 days to 26 months postoperative, and device migration within 30 days to 23 months postoperative. Timing was not reported in 1 study reporting SAEs from adhesion barriers. Studies evaluating vascular closure reported pain, bleeding, and hematoma up to 30 days postoperatively. Mesh-related responses occurred at 2 months (pain), mean 18 months (hematoma, seroma, and pain), and mean 38 months (protrusion, hernia recurrence, seroma). Hepatobiliary toxicities reported from LifePearl microspheres occurred up to 20 months postprocedure. Local responses to Hemopatch wound dressings appeared up to 3 months (seroma) and up to 6 months (epidural hematoma and pseudomeningocele). Dehiscences occurred from MembraGel bone graft from 7 to 10 days up to 18 months. Local responses with SpaceOAR were reported at 15 months to 3 years followup.

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?

Overall, 12 studies investigated systemic responses; studies addressed PEG as a material (1), sealants (4), aneurysm sealant (2), adhesion barrier (2), embolic agent (2), and hydrogel spacer (1). 10 studies identified persistent or exaggerated immune responses, while 30 studies did not investigate systemic responses.

b. What are the likely systemic manifestations?

For sealants, evidence from 4 randomized controlled trials (RCTs) reported systemic responses after sealant closure in pleural, vascular, gynecological, and spinal/cranial anatomies. Pleural-related responses included cardiac disorders (chronic cardiac failure, ventricular fibrillation), nervous system disorders (ischemic stroke), or subcutaneous tissue disorders (subcutaneous emphysema) in 1.6% of patients. Vascular-related responses also included stroke (2%) but also reported azotemia (0.9%). Gynecologic-related responses included headache (5.7%), paresthesia (2.9%), hypersensitivity (2.9%), and skin rash (5.7%). The spinal/cranial study comparing two PEG sealants reported 8 SAEs with Adherus (but not DuraSeal) including convulsion, dysphagia, headache, and respiratory failure in 0.8% of patients each.

For aneurysm sealant, systemic responses from Nellix in 2 studies (1 systematic review (SR), 1 nonrandomized comparative study) included cardiac complications, postimplantation syndrome (PIS) and PIS-related symptoms (fever, high-sensitivity C-reactive protein (CRP) elevation, leukocytosis), death, paraparesis, respiratory failure, and stroke.

For adhesion barrier, 1 RCT (n=117) reported nausea, muscle spasm, pain in extremity, and hypoaesthesia in >10% of patients using Oxiplex. Constipation, vomiting, chills, fever, arthralgia, buttock pain, muscle weakness, musculoskeletal stiffness, myalgia, dizziness, headache, hyporeflexia, sensory loss, insomnia, and pruritis in <10% of patients.

For embolic agent, post-embolization syndrome (PES) was the most common systemic response reported in 2 single-arm studies addressing transarterial chemoembolization with anthracycline-loaded LifePearl microspheres. One study reported Grade 1 to 2 adverse events in 71% of patients were "related to LifePearl" including abdominal pain (n=6), fatigue and hypertension (n=3); and diarrhea, general health alteration, and facial cutaneous lesion in 1 patient each. Additionally, mild transient increase in alanine aminotransferase (ALT, 10.3%), aspartate aminotransferase (AST, 7.2%), and bilirubin (6.2%) were reported. The other study also reported Grade 1 to 2 PES-related symptoms occurring in 42% to 70% of

patients. Symptoms included abdominal pain, fever, and nausea/vomiting. Prolonged PES (n=6) was followed by moderate abdominal pain, slightly elevated temperature, nausea/vomiting, and loss of appetite which all resolved by day 4.

For hydrogel spacer, reported systemic responses in 8 of 22 patients receiving SpaceOAR prior to radiation. Complications included pulmonary embolism (n=4), severe anaphylactic reaction (n=1), and severe urosepsis (n=1). Additionally, dizziness/nausea post-procedure leading to unresponsiveness and death, and perineal abscess with subsequent death from alcoholic cardiomyopathy occurred. In both these instances, there was an unclear association with the device.

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

For sealants, azotemia, cardiac disorders, stroke, subcutaneous emphysema, and ventricular fibrillation occurred within 30 days. Headache, hypersensitivity, paresthesia, and rash occurred within 4 to 12 weeks. Convulsion, dysphagia, headache, and respiratory failure occurred within 120 days.

For aneurysm sealant, 1 study reported PIS-related symptoms (fever, leukocytosis, high-sensitivity CRP elevation) occurred within the first 2 days after endografting, while cardiac complications occurred up to 60 months postoperatively. The other study reported mortality within 30 days of surgery, and other complications (paraparesis, respiratory failure, stroke) from 30 days to 23 months.

For adhesion barrier, all responses occurred within 6 months and also occurred with controls (surgery only).

For embolic agent, device-related PES-related symptoms occurred within day 4 postoperative.

For hydrogel spacer, responses occurred 15 months to 3 years post-SpaceOAR injection.

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

No studies investigated cellular/molecular mechanisms for systemic responses.

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 studies investigated patient-related factors that may predict, increase, or decrease the likelihood 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?**

No studies investigated material-related factors that may predict, increase, or decrease the likelihood of an exaggerated, 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 and animal RCTs for local responses to PEG as a material and for all device categories to better ascertain associations with these responses to PEG.
b. Additional research on systemic responses, including those on patient or material factors, for all PEG device categories. Systemic responses were only investigated in 12 (28%) studies with no studies investigating PEG for vascular closure, mesh, wound dressing, bone filler/grafting, dermal filler, hydrogel tissue marker, and eye surgery dye.

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. To date, in 2021, the following 12 topics were 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)

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 Polyethylene glycol?
    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 six 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

i) Local:

Inflammation
Sensitization
Irritation
    Scarring/ fibrosis
Keloid formation
Contracture
Ingrowth
    Erosion
ii) Systemic:

Cancer (lymphoma)
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 May 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 - Polyethylene glycol (PEG)

Full Name: Polyethylene glycol
CAS Registry Number: [25322-68-3]

Safety Brief - Systematic Review Results

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

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

Regulatory Description	Product Code	Class
Sealant, Polymerizing	NBE	3

Surgical Sealant, Polymerizing	NQR	3
Ophthalmic Sealant	PFZ	3
Device, Hemostasis, Vascular	MGB	3
Barrier, Adhesion, Cardiovascular	OBD	3
Inhibitor, Peridural Fibrosis (Adhesion Barrier)	MLQ	3
Mesh, surgical, polymeric	FTL	2
Mesh, surgical, non-absorbable, large abdominal wall defects	OXJ/FTL	2
Dressing, Wound, Collagen	KGN	Unclassified
Dressing, Wound, Drug	FRO	Unclassified
Splint, Intranasal Septal	LYA	1
Filler, bone void, calcium compound	MQV	2
Filler, bone void, osteoinduction (w/o human growth factor)	MQV/MBP	2
Bone grafting material.; Barrier, Synthetic, Intraoral	NPK	2
Wax, Bone	MTJ	Unclassified
Agents, embolic, for treatment of benign prostatic hyperplasia	NOY, KRD, NAJ	2
Device, vascular, for promoting embolization	KRD, NAJ	2
Absorbable perirectal spacer	OVB	2

The Safety Brief summarizes the findings of the literature search on toxicity/biocompatibility of Polyethylene glycol (PEG). 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. 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 PEG as a material as well as research on the various device categories.

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)
Polyethylene glycol (PEG) as a material (2 animal studies)	Dissemination of DBBM granules, fibrosis, hemorrhage, inflammatory reaction containing	Very low	1 study investigated, but did not identify	Very low

Application	Local Host Responses/Device Events	Quality of Evidence (local responses)	Systemic Responses	Quality of Evidence (systemic responses)
	lymphocytes and macrophages		systemic responses.	
Sealants (9 human studies)*	Bronchopleural fistula, CSF leak, drug hypersensitivity, dysmenorrhea/metrorrhagia, emphysema, fistula, foreign body sensation, grade 1 to 4 complications, hematoma, high IOP, hydropneumothorax, leaking after re-provocation, meningitis, neurological complications, ovarian cyst, pain, pericardial effusion, pleural effusion, pneumothorax, pseudomeningocele, respiratory distress, proctitis, sensation of pressure in the rectum, sudden need for defecation, thrombosis, uterine disorder	Low	Azotemia, cardiac failure, convulsion, dysphagia, headache, hypersensitivity, paresthesia, rash, respiratory failure, stroke, subcutaneous emphysema, ventricular fibrillation	Low
Aneurysm sealant (3 human studies)	Bleeding, embolus, endoleak, enlargement, hematoma, migration, occlusion, pseudoaneurysm, rupture, thrombus	Low for migration Very low for all other local responses/device events	Cardiac complications, death, paraparesis, PIS (characterized by fever, leukocytosis, and high-sensitivity CRP elevation), respiratory failure, stroke	Very low
Adhesion barrier (4 human studies)	Patency, serious adverse events (not defined)	Low	Arthralgia, chills, constipation, dizziness, fever, headache, hypoaesthesia,	Very low

Application	Local Host Responses/Device Events	Quality of Evidence (local responses)	Systemic Responses	Quality of Evidence (systemic responses)
			hyporeflexia, insomnia, muscle spasm/weakness, myalgia, nausea, pain, pruritus, sensory loss, vomiting, weakness	
Vascular closure (7 human studies)	Bleeding, hematoma, pain, retroperitoneal bleed, vascular complications	Moderate for bleeding and hematoma. Low for all other local responses/device events.	No studies investigated.	Very low
Mesh (4 human studies)	Bleeding, hematoma, hernia recurrence, pain, perforation, protrusion, seroma	Very low	No studies investigated.	Very low
Embolic agent (2 human studies)	Chronic artery occlusion and stenosis of coronary ostium artery, false aneurysm of segment V in the liver, hepatobiliary toxicities (bilomas, portal vein thromboses, portal vein branch narrowing, bile duct dilations)	Very low	Diarrhea, facial cutaneous lesion, fatigue, hypertension; increases in ALT, AST, and bilirubin; postembolization syndrome (including abdominal pain, fever, nausea/vomiting)	Very low
Wound dressing (2 human studies)	CSF leak, drain output, epidural hematoma, pseudomeningocele, seroma	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)
Bone filler/grafting (2 human studies)	Dehiscence	Very low	No studies investigated	Very low
Dermal filler	No studies	Very low (no evidence)	No studies	Very low (no evidence)
Hydrogel spacer (6 human studies)*	Bleeding, fecal incontinence, fistula, general acute and late Grade 1 and Grade 2 GI and GU toxicities, perineal abscess, perirectal fistula, proctitis, prostatic abscess, purulent drainage from perineum, rectal hemorrhage, rectal ulcer, rectal wall erosion, rectourethral fistula, tenesmus with air in rectal wall	Low	Death, dizziness/nausea leading to unresponsiveness and death, PE, severe anaphylactic reaction, severe urosepsis	Low
Hydrogel tissue marker	No studies	Very low (no evidence)	No studies	Very low (no evidence)
Eye surgery dye (1 human study)	No local responses occurred	Very low	No studies investigated systemic responses.	Very low

*One study addresses both categories

ALT: alanine aminotransferase; AST: aspartate aminotransferase; CRP: C-reactive protein; CSF: cerebrospinal fluid; DBBM: deproteinized bovine bone mineral; GI: gastrointestinal; GU: genitourinary; IOP: intraocular pressure; PIS: postimplantation syndrome

Polyethylene glycol as a Material

2 animal studies (1 RCT[1] and 1 nonrandomized comparative study[2]). For further information see Table 1 in Appendix D.

Local Responses (human studies)

We did not identify any human studies investigating local responses to PEG as a material.

Local Responses (animal studies)

1 RCT evaluated the ability of 2 synthetic membranes for guided bone regeneration and containment of 120 mg of deproteinized bovine bone mineral (DBBM) within ridge defects created after molar removal in 18 female dogs.[1] Comparators included PEG membrane plus DBBM, a resorbable glycolide carbonate membrane plus DBBM (PGA-TMC), DBBM alone, and controls. Postoperative complications included swelling in all 4 sites in 1 dog sacrificed after 2nd surgery (baseline). Additionally, marked signs of hemorrhage (28.5% PEG sites, 14.2% PGA-TMC site), membrane detachment (28.5% PEG and PGA-TMC sites each) and some dissemination of DBBM granules across all DBBM-filled sites were reported. No complications were observed at 4 or 16 weeks.

1 nonrandomized comparative study examined the use of 5% PEG 4000 and bovine amniotic membrane (BAM) to reduce adhesion formation and prevent complications of polypropylene (PP) mesh when used to repair abdominal wall hernias in 32

Wistar rats.[2] Comparisons were PP mesh (with or without BAM) plus 5% PEG 4000 as an adhesion barrier or sodium chloride (NaCl).

Results for macroscopic (adhesion severity grade), and microscopic evaluations (fibrosis and inflammation) revealed the combined use of 5% PEG 4000 plus BAM was significantly better vs. control in preventing complications up to 21 days. No significant differences were reported for 5% PEG 4000 vs. BAM and 0.9% NaCl or either group vs. control.

Macroscopic findings indicated an inflammatory reaction (containing lymphocytes and macrophages) was present in 3 cases (2 control, 1 in 5% PEG 4000). Highest adhesion percentage was noted in controls, while the lowest adhesion percentage was with 5% PEG 4000 plus BAM. Microscopic findings indicated the following:

- 5% PEG 4000 plus BAM: a very small number of inflammatory cell infiltration and fibrosis
- 5% PEG 4000: normal lymphohistiocytic infiltration and vascularization
- 0.9% NaCl and BAM: medium inflammatory cell infiltration and fibrosis
- 0.9% NaCl: fibrous adhesions and foreign body giant cells and fibrosis

Systemic Responses

One RCT investigated but did not identify any systemic responses from PEG as a material.[1]

Factors Associated with Systemic Responses

One RCT investigating systemic responses, did not report whether there are patient-related factors or material-related factors that may affect systemic responses.[1]

Overall Quality of Evidence

The 2 animal studies, both with control groups, were inconsistent in reporting hemorrhage and fibrosis, and these findings are inconsistent with findings from other PEG devices used in humans. Considering these factors, we rated the quality of evidence as very low. We also rated the quality of evidence for systemic responses as very low.

Sealants

9 human studies (2 systematic reviews (SRs),[3,4] 5 RCTs,[5-9] 1 nonrandomized comparative study,[10] and 1 single-arm study [11]). For further information see Table 2 in Appendix D.

Local Responses/Device Events (human studies)

Studies analyzed sealants as a means of closure in ocular[3], pleural[7,10], vascular[5], gynecological[8], spinal/cranial[6,9,11], and rectal[4] anatomies. Follow-up ranged from immediately postoperative to 60 months, with study size of 66 to 347 patients. One study examined pediatric patients.[11]

Patients in the corneal-focused SR,[3] examining ReSure and OcuSeal sealants, reported higher immediate post-operative intraocular pressure with ReSure compared to self-sealing, as well as a higher pain score with ReSure compared to collagen treatment. OcuSeal had lower surgically induced astigmatism and foreign body sensation compared to sutured closure.

Two studies focusing on pleural closure[7,10] examined standard closure vs. ProGel[10] or PleuraSeal.[7] The most commonly reported local response was pneumothorax (rate of 8.1%[7] to 40.5%[10]). One study reported similar pneumothorax rates within 90 minutes postoperative (40.5% ProGel, 37% standard closure).[10] Less frequently reported local responses up to 30 days postoperatively in the other study[7] included bronchopleural fistula (1.6%), emphysema (1.6%), pain (3.2%), pleural effusion (1.6%), respiratory distress (1.6%), and hydropneumothorax (1.6%). Patients in the control group did not display these symptoms aside from hydropneumothorax (3.4%).

One patient in the vascular-focused RCT[5] reported pericardial effusion from Tridyne (0.9%), which was not reported in the control group; followup was 30 days postoperative.

2.9% of patients reported the following in the gynecological study using Actamax[8]: abdominal pain, drug hypersensitivity, dysmenorrhea/metrorrhagia, ovarian cyst, or uterine disorder. Pain and cysts were also reported in the control group (3.2%). Followup was 4 to 12 weeks at second-look laparoscopy.

Local responses reported in the spinal/cranial studies using DuraSeal[6,9,11] and Adherus[9] were hematoma (rate of 0.8% with Adherus[9]), pseudomeningocele (0.8% DuraSeal, 2.4% Adherus[9]), intracranial venous sinus thrombosis (0.8% DuraSeal, 0%

Adherus[9]), cerebrospinal fluid leak (11.0% DuraSeal, 12.5% controls[6]), neurological complications (6.8% DuraSeal, 8.3% controls[6]), and meningitis (0.6% DuraSeal[11]). Followup was 90 days,[6,11] and 120 days.[9]

A rectal spacer-focused SR[4] examined performance of PEG sealant with DuraSeal (reported here) and a PEG hydrogel spacer (see section on Hydrogel spacer) with a median followup ranging from 6 to 60 months. 1 nonrandomized comparative study (100 patients with DuraSeal vs. 100 patients without DuraSeal) reported no complications. Results from 3 single-arm studies included acute and late gastrointestinal (GI) toxicities. Acute GI toxicities from two smaller single-arm studies (n=10, n=11) included 9% grade 2 toxicity (fistula) and sensation of pressure in the rectum and sudden need to defecate in 1 patient each. In a large cohort with over 300 patients, acute toxicity events were more common with 37.4% reporting Grade 1 complications and 2.8% reporting Grade 2 complications. Late GI toxicity was more common with one small study (n=11) having 36% report Grade 1 or 2 complications, and 9% having Grade 3 or 4 complications. 1 patient had a prostatorectal fistula requiring a diverting colostomy. The large cohort study had 12.7% Grade 1 complications, 1.4% Grade 2 complications, 0.7% Grade 3 complications, 1 case of severe proctitis, and 1 case of a fistula requiring colostomy.

Local Responses/Device Events (animal studies)

We did not identify any animal studies investigating local responses to PEG as sealants.

Systemic Responses

4 RCTs analyzed sealants as a means of closure in pleural[7], vascular[5], gynecological[8], and spinal/cranial[9] anatomies. Follow-up ranged from discharge to 120 days, with sample size of 35 to 126 patients.

In the pleural study[7], the incidence of complications was similar between PEG and control groups. 1.6% of patients in the PEG group reported chronic cardiac failure, ischemic stroke, or subcutaneous emphysema.

In the vascular study[5], two patients each in the PEG and non-PEG control exhibited stroke (2% versus 4%, respectively). One patient (0.9%) in the PEG group exhibited azotemia (excess of urea or other nitrogenous wastes in the blood as a result of kidney insufficiency).

In the gynecological study[8], patients reported headache (5.7% versus 6.5% in the control group), paresthesia (2.9% versus 0%), hypersensitivity (2.9% versus 3.2%), and skin rash (5.7% versus 0%).

The spinal/cranial study compared two different PEG sealants.[9] Serious adverse events (SAEs) in each group were mild or moderate and over 50% had resolved by 120-day follow-up. Eight SAEs occurring with Adherus (but not DuraSeal) included convulsion (0.8%), dysphagia (0.8%), headache (0.8%), and respiratory failure (0.8%).

Overall Quality of Evidence

The evidence for most outcomes was inconsistent across studies however >50% studies had control groups, so the quality of evidence is low. For systemic responses, the quality of evidence is also low.

Aneurysm sealant

3 human studies (2 SRs,[12,13] and 1 nonrandomized comparative study[14]). For further information see Table 3 in Appendix D.

Local Host Responses (human studies)

Two SRs examined outcomes associated with endovascular aneurysm sealing (EVAS) with the Endologix Nellix device. The reviews consisted of single-arm studies or case reports examining approximately 1550 patients overall with asymptomatic abdominal aortic aneurysm (AAA)[13] or prior endovascular abdominal repair (EVAR).[12] Gender was not consistently reported and ages ranged from 70 to 87 years. Follow-up ranged from 30 days to 26 months.

Local responses for EVAS following EVAR in 1 SR[12] were new endoleaks in 9.8% of patients ranging from type Ia (diagnosed 5-months post-surgery) to type II (diagnosed 5 to 26 months post-surgery). One study had a patient with a post-operative hematoma and pseudoaneurysm. Three studies specifically noted no graft thrombosis or chimney graft occlusion. Of 11 included studies, 7 (64%) were case reports.

The most commonly reported local responses for EVAS for asymptomatic AAA[13] reported in the other SR were aneurysm rupture within 30 days of surgery (8 studies, 0 to 2% rate), aneurysm rupture in 1 to 23 month follow-up (12 studies, 0 to 1.3% rate), endoleak within 30 days of procedure (49 of 1,510 patients, 59% Type I), migration within 30 days (5 studies, 0 to 6.7% rate), and migration in 5 to 23 months follow-up (9 studies, 0 to 13% rate). This SR included 14 single-arm studies.

Less frequently reported local responses were sac enlargement, thrombus formation, groin hematoma, artery occlusion, embolus formation, and duodenal bleeding.

Local Host Responses (animal studies)

We did not identify any animal studies investigating local responses to PEG as aneurysm sealants.

Systemic Responses

Two studies[13,14] reported systemic responses from Nellix.

A nonrandomized comparative study investigated responses from EVAS with Nellix versus EVAR with 2 devices (Gore Excluder, Endologix) composed of expanded polytetrafluoroethylene (ePTFE).[14] Postimplantation syndrome (PIS) occurred in both groups within 2 days of endografting (13.8% EVAS, 38.7% EVAR; p=0.001). Symptoms included fever (8.6% EVAS, 34.5% EVAR), leukocytosis (12.1% vs. 20.8%), and high-sensitivity C-reactive protein elevation (46.6% vs. 72.7%). New onset thrombosis was reported in both ePTFE devices (21% Gore Excluder, 14% Endologix), but did not occur with Nellix. Additional complications up to 60 months included cardiac complications (15.5% EVAS, 36% to 41% EVAR) and unspecified non-cardiac complications (44.8% EVAS, 36% to 41% EVAR).

The most commonly reported systemic responses for EVAS for asymptomatic AAA[13] in a SR were mortality within 30 days of surgery (0 to 4.8% rate) with 7 out of 10 deaths being non-device related, and respiratory failure (3 studies). Other reported complications were stroke (1 study), PIS (5 cases in 1 study), and paraparesis (1 study).

Overall Quality of Evidence

The evidence for migration was consistently reported in one SR; however, because of the low quality of the individual studies and disagreement with reporting with other PEG devices, the quality of evidence is low. For other local responses/events and systemic responses, the quality of evidence is very low.

Adhesion barrier

4 human studies (1 SR,[15] 2 RCTs,[16,17] and 1 nonrandomized comparative study[18]). For further information see Table 4 in Appendix D.

Local Responses/Device Events (human studies)

One SR[15] examined incidence of serious adverse events (SAEs) with different barrier devices including PEG devices (SprayGel, SprayShield), hyaluronate carboxymethylcellulose (Seprafilm®) oxidized regenerated cellulose (Interceed®) and icodextrin 4% solution (Adept®). Six out of 7 PEG-device studies had 100% female patients, no mean age reported. Study size for SprayGel ranged from 11 to 72 patients. Authors reported overall SAEs in 3 studies with Spraygel were limited and similar versus controls. Evidence for one non-PEG barrier (Seprafilm®) included treatment wrapping around a new bowel anastomosis which may have resulted in a higher incidence of SAEs including abscesses, fistulas, and anastomotic leakages.

Two studies examined outcomes associated with use of a surgery plus a PEG sealant (Oxiplex,[17] Intercoat[18]) versus treatment with surgery alone in single-level lumbar discectomy[17] (51% female, mean age 42 years) and hysteroscopic surgery[18] (100% premenopausal women). Study size was 110 patients[18] and 341 patients,[17] and follow-up was 1 and 6 months.[17]

In one RCT[17], 24.9% of patients and 2.4% patients reported back pain and disc protrusion from discectomy, respectively, but no adverse events were attributed to device use. In the nonrandomized comparative study,[18], one patient (2.1%) reported worsening patency of the uterine ostium at one month post-hysteroscopy in comparison to 10 patients in the control group.

Local Responses/Device Events (animal studies)

We did not identify any animal studies investigating local responses to PEG as adhesion barriers.

Systemic Responses

One RCT[16] reported two serious adverse events (dehydration and fasciitis) with 50% of subjects in the PEG device group experiencing at least 1 adverse event, but no adverse events were attributed to device use.

A second RCT[17] examined patients (n=171, 51% female) undergoing single-level lumbar discectomy with and without an adhesion barrier with 6 months follow-up. Patients reported constipation (6.8%), nausea (19.8%), vomiting (5.6%), chills (4.5%), fever (4.5%), arthralgia (6.8%), buttock pain (6.8%), muscle spasm (14.1%), muscle weakness (5.1%),

musculoskeletal stiffness (5.1%), myalgia (3.4%), pain in extremity (14.7%), dizziness (5.6%), headache (7.9%), hypoaesthesia (10.2%), hyporeflexia (5.1%), sensory loss (2.3%), insomnia (6.8%), and pruritis (4.5%) with Oxiplex. Investigators noted that no SAEs were due to barrier use.

Overall Quality of Evidence

For local responses, most studies described either similar responses versus controls or did not attribute the responses to the PEG device; however the quantity of evidence was limited so we rated the quality of evidence as low. For systemic responses, the quality of evidence was rated very low.

Vascular closure

7 human studies (2 SRs,[19,20] 1 RCT,[21] 4 nonrandomized comparative studies[22-25]). For further information see Table 5 in Appendix D.

Local Host Responses (human studies)

Evidence on PEG as a vascular closure device examined either Mynx or MynxGrip devices (both developed by AccessClosure, Inc.); over 75,000 patients received a PEG device in 6 studies reporting enrollment. Follow-up ranged between 30 days and 12 months post-operation in five studies, two studies had unclear follow-up times.[20,21] All patients underwent a unilateral or bilateral insertion of the PEG device, originating either at the common femoral artery (CFA) or superior femoral artery (SFA).

One SR[20] meta-analyzed 27 studies relating to 7 vascular closure devices. Devices included PEG devices (Mynx, MynxGrip) and six non-PEG devices (Angioseal, Exoseal, Femoseal, Glubran 2, Perclose, Starclose). Evidence for PEG included bleeding-related complications (e.g., access site bleeding/hematoma or retroperitoneal bleed) and overall complications (e.g., vessel occlusion or stenosis, embolization, pseudoaneurysm formation, arteriovenous fistular formation, and bleeding-related complications) using the CFA approach. Rates for overall complications (range, 0.9% Mynx to 7.4% Starclose) and bleeding-related complications (range, 0.4% Mynx to 7.2% Femoseal) were lowest with Mynx.

The other SR[19] qualitatively analyzed patients undergoing a single surgery using a PEG (MynxGrip) or non-PEG device (AngioSeal, Arstasis, Boomerang, Cardiva, Catalyst II, Exoseal, Ensure Medical VCD, FemoSeal, FISH, Perclose ProGlide, ProStar, ProStar XL, StarClose, Vascade). The review contained three studies specifically examining MynxGrip. One nonrandomized comparative study found patients experienced less pain with MynxGrip compared to AngioSeal. Another nonrandomized comparative study found low incidence of vascular complications, comparable to other vascular closure devices, specifically AngioSeal and Perclose. Lastly, an included single arm study found low incidence of vascular complications. All other non-PEG studies found generally low incidences of AEs, mainly regarding vascular complications.

One RCT[21] examining patients undergoing a single insertion into the CFA reported no complications with MynxGrip (n=103) or manual compression (n=104).

Three nonrandomized comparative studies all with 30-day followup compared adverse event rates with Mynx (>1800 patients) versus non-PEG devices (including AngioSeal, ExoSeal, Perclose, Starclose, FISH) or manual compression techniques.

Results from 2 studies comparing Mynx with several non-PEG devices indicated:

- Rates for minor complications ranged from 1.3% to 5.7%; Mynx rate of 2.3% included minor hematomas (n=6), minor bleeding (n=3), and extended recovery (n=5). Thrombosis only occurred with manual compression. Rates for major complications ranged from 0% to 1.3%; Mynx rate of 0.7% included major hematoma (n=2), major bleeding (n=1), and retroperitoneal bleeding (n=1).[23]
- Rates for major complications (possibly due to pseudoaneurysm, bleeding/hematoma, arterial stenosis) were low and ranged from 0% to 1.9%; Mynx rate of 1.8%. Rates for total complications (mostly minor bleeding or small hematomas) ranged from 1.8% to 14.5%; Mynx rate highest however this may be due a higher enrollment of cirrhotic patients.[25]

Results from 1 study comparing Mynx with AngioSeal[22] indicated rates of vascular injury were higher with Mynx (0.8% vs. 0.3%) whereas, access-site bleeding was higher with AngioSeal (1.9% vs. 1.4%).

Lastly, one nonrandomized comparative study[24] examined over 150,000 patients (73,124 received Mynx). Results indicated slightly higher access-site bleeding (0.4% Mynx, 0.3% other devices), post-procedural blood transfusion (1.8% Mynx, 1.5%

other device), and vascular complication rates (1.2% Mynx, 0.8% other devices) in Mynx compared to alternative vascular closure devices up to 12 months.

Local Host Responses (animal studies)

We did not identify any animal studies investigating local responses to PEG as vascular closure.

Systemic Responses

We did not identify any studies reporting systemic responses to PEG as a vascular closure device.

Overall Quality of Evidence

The evidence for bleeding and hematoma were consistently reported across higher-quality studies with large enrollment and in agreement with reporting with other PEG devices (e.g., aneurysm sealant, mesh) so we rated the evidence as moderate. For other local responses/events, the quality is low. For systemic responses, the quality of evidence is very low.

Mesh

4 human studies (1 SR,[26] 1 RCT,[27] 1 nonrandomized comparative study,[28] and 1 single arm study[29]). For further information see Table 6 in Appendix D.

Local Responses/Device Events (human studies)

The SR[26] included 33 studies of stoma site incisional hernias, but only 4 of the studies provided data on prophylactic mesh, and of those, only 1 used PEG. That study was a case series (n = 10) that reported, "No serious mesh-related or other serious complications were observed during 12 month follow-up."

The RCT[27] examined 54 women undergoing laparotomic myomectomy; to prevent adhesions, women were randomized to receive either PrevAdh (Covidien), which is a resorbable dual-sided membrane with one side containing PEG (n = 28), or 500 mL Ringer's lactate solution instilled into the pelvic cavity (n = 26). The study reported no device-related complications occurred during 3 years of follow-up in either group.

The nonrandomized comparative study[28] examined 393 patients undergoing open inguinal hernia surgery in which self-adhering synthetic mesh was used to support the inguinal canal's muscular layer. The mesh used was either Adhesix (Cousin Biotech), which is a 7.5 × 15.5 cm glued mesh with a PEG-containing coating (n = 169), or Parietex ProGrip (Medtronic), which is a 12 × 8 cm polyester/polylactic gripping mesh (n = 224). The surgeries were performed by one surgeon who used ProGrip exclusively and another who used Adhesix almost exclusively. During a mean follow-up of 18 months (Adhesix) or 19 months (ProGrip), the study reported no significant difference between the Adhesix and ProGrip groups in rates of hematoma (1.2% versus 1.8%) or seroma (0.6% versus 0.9%); however, patients in the Adhesix group were significantly less likely to contact providers due to pain than were patients in the ProGrip group (2.4% versus 8.5%, p = 0.01). The study reported no hernia recurrence during follow-up in either group.

The remaining study[29] was a single arm study (n = 107) of patients undergoing laparoscopic ventral hernia repair, comparing two surgical approaches (closure versus non-closure of the fascia defect) and two fixation techniques (one ring of ProTack non-absorbable tackers and four corner stay-sutures versus two rings of tackers). All patients received Parietex Composite mesh (Medtronic), which contains PEG. During a mean of 38 months of follow-up, the study reported the following AE rates: mesh protrusion, 10.3%; hernia recurrence, 2.8%; reoperations for bleeding and perforation, 1.9%; seroma, approximately 12%. In addition, 27.1% of patients reported pain at 2 months post procedure.

Local Responses/Device Events (animal studies)

We did not identify any animal studies investigating local responses to PEG as mesh.

Systemic Responses

We did not identify any studies investigating systemic responses to PEG as mesh.

Overall Quality of Evidence

For local responses, evidence was inconsistent across studies with 50% of studies being low quality, so we rated the quality of evidence as very low. For systemic responses, the quality of evidence was also rated very low.

Embolic agent

2 human studies (2 single arm studies[30,31]) examined patients with hepatocellular carcinoma (HCC) undergoing transarterial chemoembolization (TACE) with drug-eluting microspheres (DEM-TACE) or drug-eluting beads (DEB-TACE), a procedure that simultaneously embolizes tumor feeding arteries and delivers anticancer drugs. Both studies addressed anthracycline-loaded microspheres made of polyethylene glycol (PEG) (LifePearl™, Terumo Europe) in mostly males aged over 55 years. Overall, studies enrolled 117 patients, 241 TACE procedures, using LivePearl doses of 100 to 200 microns with followup to 12 months,[31] and 20 months.[30] For further information see Table 7 in Appendix D.

Local Responses/Device Events (human studies)

The first study examined 97 patients with Barcelona Clinic Liver Cancer (BCLC) Stage A (early) and B (intermediate) HCC undergoing DEM-TACE with LifePearl microspheres loaded with doxorubicin (77%) or idarubicin (23%).[30] 187 DEM-TACEs were investigated; 54.6% of patients underwent ≥2 DEM-TACE. Serious adverse events (SAEs, Grade ≥3) "related to LifePearl" included false aneurysm of segment V in the liver, and chronic artery occlusion and stenosis of coronary ostium artery in 1 patient each. In addition, hepatobiliary toxicities (HBTs) were reported in 29 (30%) patients undergoing mean 2.4±1.4 DEM-TACE. HBTs included bilomas (abnormal collection of bile outside the gallbladder) in 7 patients, portal vein thromboses in 4 patients, and bile duct dilations in 8 patients up to 20 months post DEM-TACE. 10 (34%) patients experiencing HBTs had 1 to 7 prior liver-directed therapies (e.g., thermal ablations, prior DEM-TACE).

The second study examined 20 patients with mostly BCLC Stage A and B HCC undergoing DEB-TACE with doxorubicin-loaded LifePearl microspheres.[31] No local responses to LifePearl were reported up to 12 months.

Local Responses/Device Events (animal studies)

We did not identify any animal studies investigating local responses to PEG as embolic agents.

Systemic Responses

Postembolization syndrome (PES), a systemic response characterized by fever without associated sepsis, right upper quadrant abdominal pain, and nausea and/or vomiting was the most commonly reported adverse event in both studies.

The first study reported PES-related Grade 1-2 adverse events in 71% patients.[30] 21 SAEs (Grade ≥ 3) reported in 13 (13.4%) patients and "related to LifePearl" were abdominal pain in 6 patients, fatigue and hypertension in 3 patients each, and diarrhea, general health alteration, and a facial cutaneous lesion in 1 patient each. Additionally, mild transient increase in alanine aminotransferase (ALT, 10.3%), aspartate aminotransferase (AST, 7.2%), and bilirubin (6.2%) were reported.

The second study reported that Grade 1 or 2 PES rates following DEB-TACE ranged from 42% (after 2nd DEB-TACE) to 70% (after 3rd DEB-TACE).[31] Occurrence of PES symptoms after 1st DEB-TACE (n=20) to 5th DEB-TACE (n=2) included abdominal pain in 21% to 60% of patients, fever in 5% to 50% of patients, and nausea/vomiting in 5% to 33.3% of patients. Prolonged PES reported in 6 patients was followed by moderate abdominal pain, slightly elevated temperature, nausea/vomiting, and loss of appetite, which were all resolved by day 4.

Overall Quality of Evidence

The evidence for local responses was inconsistent across studies and based on low quality studies, so the quality of evidence is very low. For systemic responses, the quality of evidence was also very low.

Wound dressing

2 human studies (2 nonrandomized comparative studies[32,33]). For further information see Table 8 in Appendix D.

Local Responses/Device Events (human studies)

One nonrandomized comparative study[32] examined 147 patients undergoing cranial and intradural spinal procedures using either of two hemostatic pads – Hemopatch (Baxter), which contains PEG (n = 82), or Tisseel (Baxter), which does not (n = 65). The study reported cerebrospinal fluid leak rates of 3.6% for Hemopatch and 13.8% for Tisseel ($p < 0.05$ in bivariate and multivariate analyses), epidural hematoma rates of 18.3% (15/82) for Hemopatch and 18.5% (12/65) for Tisseel ($p = 0.98$ in

bivariate analysis), and pseudomeningocele rates of 9.75% for Hemopatch and 21.5% for Tisseel (p = 0.06 in bivariate analysis, p = 0.14 in multivariate model). Followup was at least 6 months.

The other nonrandomized comparative study[33] examined 60 patients undergoing total thyroidectomy using a harmonic scalpel and either Hemopatch (n = 30) or standard hemostasis (gauze, ligature, electrocauterization) (n = 30). The study reported patients receiving Hemopatch had significantly lower 24-hour drain output than patients receiving standard hemostasis (50.1 mL versus 90.3 mL, p <0.0001). Up to 3 months followup, the incidence of postoperative seroma was higher in the standard hemostasis group, but did not report the actual rates. In addition, no surgical or postsurgical complications occurred in the Hemopatch group, whereas three patients in the standard hemostasis group had surgical complications (not specified) and two developed temporary laryngeal nerve paralysis.

Local Responses/Device Events (animal studies)

We did not identify any animal studies investigating local responses to PEG as wound dressings.

Systemic Responses

We did not identify any studies investigating systemic responses to PEG as wound dressings.

Overall Quality of Evidence

Two nonrandomized comparative studies reported various complications from 1 of 6 wound dressings of interest, so we rated the quality of evidence as very low. Since systemic responses were not investigated in these studies, the evidence is also very low.

Bone filler/grafting

2 human studies (2 RCTs[34,35]). For further information see Table 9 in Appendix D.

Local Responses/Device Events (human studies)

One RCT[34] examined 117 patients receiving implants in the posterior maxilla or mandible with expected buccal bony dehiscence-type defects at the placed titanium implants. Defects were filled with synthetic bone filler and covered with either PEG (Straumann MembraGel, Straumann AG; n = 60) or native porcine-derived collagen membrane (Geistlich BioGide, Geistlich Biomaterials AG; n = 57). The number of patients in the PEG group with dehiscences were 4 at 7-10 days, 4 at 12-14 days, 3 at 4 weeks, 3 at 3 months, 2 at 6 months, and 1 at 18 months. For BioGide, the numbers were 8, 8, 7, 6, 4, and 0. Differences between the groups were not statistically significant. 30 adverse events were noted overall, including inflammation, swelling, allergy, pain, cancer, and cerebral infarction, among others. Thirty percent of all PEG patients had adverse events, compared to 10.5% of all BioGide patients.

The other RCT[35] examined 36 patients receiving implants in the posterior maxilla or mandible with expected osseous defects. Defects were grafted with deproteinized bovine bone material and covered with either MembraGel (n = 18) or BioGide (n = 18). At follow-up (1 year and 3 years after implant loading), no dehiscences were observed in either group, and periodontal status was normal in all patients.

Local Responses/Device Events (animal studies)

We did not identify any animal studies investigating local responses to PEG as bone filler/grafting.

Systemic Responses

We did not identify any studies investigating systemic responses to PEG as bone filler/grafting.

Overall Quality of Evidence

Evidence for local responses was in disagreement in 2 nonrandomized comparative trials (<100 studied) reporting on 1 of 9 PEG bone fillers/grafts of interest, so the quality of evidence is very low. Since systemic responses were not investigated in these studies, the evidence is also very low.

Hydrogel spacer

6 human studies (3 SRs,[4,36,37] and 3 nonrandomized comparative studies[38-40]). For further information see Table 10 in Appendix D.

Local Responses/Device Events (human studies)

All evidence in hydrogel spacers examined SpaceOAR devices (developed by Boston Scientific/Augmenix) with followup from 12 weeks to 60 months. Over 600 male patients with localized prostate cancer received SpaceOAR as a prostate-rectal spacer; only 1 SR examined patients before radiotherapy.[37]

One SR[37] reporting data from MAUDE found 25 total patients with AEs relating to SpaceOAR placement prior to radiotherapy; followup from 15 months to 3 years. The most commonly reported events were perineal abscess requiring drainage (n=3), and rectourethral fistula requiring colostomy (n=3). Additional complications included Level II harms (purulent drainage from perineum requiring antibiotics) and Level III harms (perirectal fistula requiring surgical intervention, proctitis requiring colostomy, rectal ulcer and hemorrhage requiring surgery, and prostatic abscess requiring drainage) in 1 patient each.

Another SR[36] qualitatively described complications relating to prostate-rectal spacing with SpaceOAR and two non-PEG devices (collagen and hyaluronic acid) with followup up to 12 months. The five studies in the SR focusing on SpaceOAR reported various AE occurrences; with the most common being grade 1 acute gastrointestinal (GI) toxicity (39.6%) or genitourinary (GU) toxicities (41.7%). Most common late toxicities were also grade 1 (4.3 % GI, 17% GU). Diarrhea and urinary obstruction were commonly reported in the non-PEG studies.

Lastly, one SR[4] qualitatively described AEs between 6 to 60 months followup for patients receiving either SpaceOAR (n=254) or DuraSeal versus patients not receiving either PEG device. DuraSeal AEs are further described in our section on Sealants. The 5 nonrandomized comparative studies in this SR focusing on SpaceOAR found mixed evidence reported on incidence of grade 1 and grade 2 complications, with no study reporting Grade 3 or 4 complications.

One nonrandomized comparative study[40] comparing SpaceOAR (n=75) to multiple administrations of rectal balloons (n=192) found significantly higher grade 1 bleeding complications in the rectal balloon arm, whereas, there was no difference in grade 2 bleeding complications. A few patients in the rectal balloon arm reported grade 3 bleeding events, and no patients had grade 4 bleeding complications.

The last two nonrandomized comparative studies reported on the same patient population, but since they gave different followup data, both studies were extracted as evidence. Both studies compared SpaceOAR to non-SpaceOAR devices and utilized different doses of radiation therapy (V40 Gray < 35%, V65 Gray < 17%, V75 Gray < 10%). The first study[38] examined AEs up to 12 weeks, and found higher incidence during radiation therapy than in the 12-week followup. The most common AEs at 12-weeks were grade 1 diarrhea and grade 1 hemorrhoids. The other study[39] noted at the 3-year followup that SpaceOAR patients had many more grade 1 hemorrhoids with all other AEs being similar to the 12-week time point.

Local Responses/Device Events (animal studies)

We did not identify any animal studies investigating local responses to PEG as hydrogel spacers.

Systemic Responses

One SR reported systemic responses in 8 of 22 patients receiving SpaceOAR prior to radiation therapy. Complications reported in the MAUDE database included pulmonary embolism (n=4), severe anaphylactic reaction (n=1), and severe urosepsis (n=1). Additionally, dizziness/nausea post procedure leading to unresponsiveness and death, and perineal abscess with subsequent death from alcoholic cardiomyopathy occurred. In both these instances, there was an unclear association with the device.[37]

Overall Quality of Evidence

For local responses, most studies described either similar responses versus controls or did not attribute the responses to the PEG device; however the quantity of evidence was limited so we rated the quality of evidence as low. For systemic responses, the quality of evidence was rated very low.

Eye surgery dye

1 human study (1 nonrandomized comparative study[41]). For further information see Table 11 in Appendix D.

Local Responses/Device Events (human studies)

1 nonrandomized comparative study examined ILM-Blue™ and MembraneBlue-Dual™ in 127 patients (127 eyes) undergoing macular surgery.[41] Both eye surgery dyes are 4% PEG and manufactured by D.O.R.C. International. The population was 55% male, with a mean age of 68 years. A second dye application of 0.1 ml was applied to the macula of 21 (33%) individuals

receiving ILM-Blue, and 25 (40%) individuals receiving MembraneBlue-Dual. No complications or side effects were observed up to 12 months.

Local Responses/Device Events (animal studies)

We did not identify any animal studies investigating local responses to PEG as eye surgery dye.

Systemic Responses

No studies investigated systemic responses to PEG as eye surgery dye.

Overall Quality of Evidence

One nonrandomized comparative study reported no complications from two relevant eye surgery dyes, so we rated the quality of evidence as very low. Since systemic responses were not investigated in this study, the evidence is also very low.

ECRI Surveillance Data

The most common complications reported within surveillance data for PEG were associated with vascular closure devices resulting in hemorrhage/hematoma and device malfunction/failure. 12 of these PSO reports indicated harm to the patient and there were no described deaths. Two PRN reports detail that after deployment the vascular access closure devices balloons deflated and ruptured causing the vascular closure to fail. 21 manufacturer issued alerts describing problems with reconstitution difficulty, failure to gel appropriately, mislabeling, air leak, product failure and updated IFU, improper transport conditions, compromised sterility, risk of ignition, high viscosity and breakage, and particles in liquid. There were no accident investigation associated with PEG.

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

Patient Safety Organization

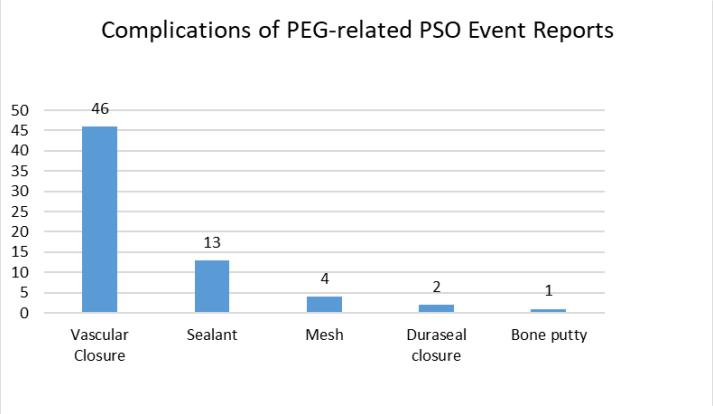
Search Results: ECRI PSO identified 447 reports that involved PEG materials that occurred between October 2015 and December 2020. 66 of these involved complications. The top 5 complications included: 1) Hemorrhage/Hematoma - 25 (37.9%), 2) Device malfunction/failure - 19 (28.8%), 3) Durotomy - 10 (15.2%), 4) CSF leak 4 (6.1%), and 5) Expired – 2 (3.0%). 18 reports resulted in harm to the patient. Nearly 70% of the PSO reports were associated with vascular closure devices including all reports of hemorrhage and 90% of device malfunction/failure (17 of 19 reports). 22 of reports associated with vascular closure devices resulted in no harm (harm scores of C and D), 8 required intervention (harm score of E), 2 required hospitalization (harm score of F) and 2 resulted in permanent harm (harm score of G). Also of note is 10 reports of durotomy associated with sealants, three of which led to harm (harm scores of E and F).

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

Table 3: Complications in PEG-related PSO Event Reports

Complication	Bone putty	Duraseal closure	Mesh	Sealant	Vascular Closure	Total
Hemorrhage/Hematoma					25	25
Device malfunction/failure			2		17	19
Durotomy				10		10
CSF leak		2		2		4

Complication	Bone putty	Duraseal closure	Mesh	Sealant	Vascular Closure	Total
Expired	1			1		2
Allergic reaction					1	1
Retroperitneal Bleed					1	1
Pseudo aneurysm					1	1
Extravasation of urine			1			1
Anastomotic leak			1			1
Limb ischemia					1	1
Total	**1**	**2**	**4**	**13**	**46**	**66**



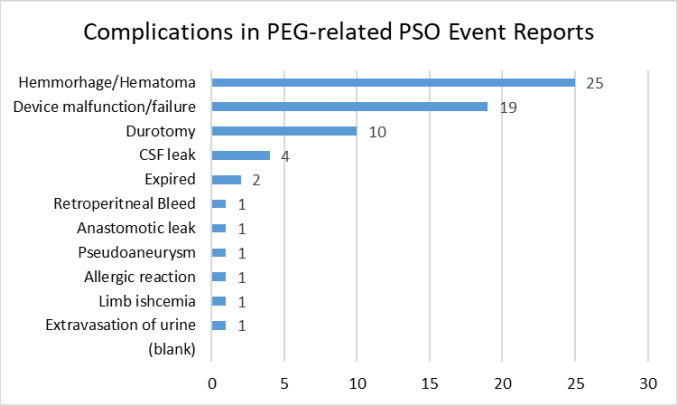


Table 4: Harm score associated with PEG-related event reports

Harm Scores (NCC-MERP)		Bone putty	Duraseal closure	Mesh	Sealant	Vascular Closure	Total
A	No Error				5	1	6
B1	Error, No Harm						
B2	Error, No Harm						
C	Error, No Harm			2	1	9	12
D	Error, No Harm	1			3	13	17
E	Error, Harm			2	2	8	12
F	Error, Harm		1		1	2	4
G	Error, Harm					2	2
H	Error, Harm						
I	Error, Death						
NULL*			1		1	11	13
Total		**1**	**2**	**4**	**13**	**46**	**66**

**Harm score was not reported*

Accident Investigations

Search Results: No investigations were recovered involving PEG-related devices.

ECRI Problem Reports

Search Results: The search returned 2 reports submitted by ECRI members.

Key Issues: The reports detail that after deployment the vascular access closure devices balloons deflated and ruptured causing the vascular closure to fail.

Safety Concerns: The reports detailed that the vascular closures failed because of balloon malfunctions.

All problem reports are redacted and included in Appendix F

Table 5: ECRI Problem Report Summary

Device Type	# Problem Reports	Reported Problem (number problem reports)
MGB (Hemostasis, Vascular)	2	• Balloon deflated • Balloon ruptured

Healthcare Technology Alerts

Search Results: The search returned 21 manufacturer issued alerts describing problems with reconstitution difficulty, failure to gel appropriately, mislabeling, air leak, product failure and updated IFU, improper transport conditions, compromised sterility, risk of ignition, high viscosity and breakage, and particles in liquid, summarized in Table 7.

Table 6: Summary of Regulatory and Manufacturer Alerts

Device Type	# Alerts	Reported Problem
NBE (Sealant, Polymerizing)	6 Manufacturer issued	• Reconstitution difficulty due to incomplete dissolution or due to temperature deviation during shipment • Failure to gel appropriately (18 month study) • Mislabeled expiration date
Sealant (outside US)	1 Manufacturer issued	• Air leak after pulmonary resection
Aneurysm Sealant (outside US)	4 Manufacturer issued	• Updated IFU to warn of higher than anticipated rates of failure due to migration, endoleak, or aneurysm enlargement • Updated IFU to warn of early polymer curing • Updated IFU to warn of prefill safety issues
MGB (Device, Hemostasis, Vascular)	1 Manufacturer issued	• Improper transport conditions
Mesh (outside US)	4 Manufacturer issued	• Compromised sterility • Mislabeling
FTL (Mesh, Surgical, Polymeric)	1 Manufacturer issued	• Mislabeling
MTJ (Wax, Bone)	1 Manufacturer issued	• May ignite if it comes into contact with cautery
Bone Filler (outside US)	1 Manufacturer issued	• Products exceed limit for viscosity which can lead to breakage
NOY (Agents, Embolic for Treatment of BPH); KRD (Device, Vascular, for Promoting Embolization); NAJ (Agents, Embolic, for Treatment of Uterine Fibroids)	1 Manufacturer issued	• Mislabeling that may lead to product migration due to misinterpretation of microsphere size
Intraocular Dye (outside US)	1 Manufacturer issued	• Particles observed in eye vitreous body following injection

Potential Gaps

ECRI surveillance searches reflect mostly acute patient incidents that involved medical devices made of PEG. 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.

PEG as a Material

2 animal studies with control groups investigated PEG as a material. The quality of evidence was considered very low for both local and systemic responses. Local responses such as hemorrhage and fibrosis were inconsistently reported between studies and inconsistent with findings from other PEG devices, and only 1 study examined systemic responses. Limitations included enrollment of only 50 animals overall, short followup (21 days) and reporting of administered dose in only 1 (50%) study, each.

Sealants

9 human studies addressing 8 different PEG sealants reported over 20 different complications with sealant closure in various anatomies. The quality of evidence of all responses benefitted from the quantity and high quality of the studies which resulted in a low rating. Limitations included only 1 (12%) study comparing PEG with a non-PEG device, only 7 (78%) studies measured complications up to 12 weeks (2 studies only preoperatively) and administered dose only being reported in 2 (22%) studies.

Aneurysm sealant

Of 3 human studies addressing 1 PEG aneurysm sealant of interest (Nellix), evidence from 2 SRs mostly consisted of single arm studies and case reports of patients aged 70 to 87 years, so we are unable to determine the direct association of most complications with PEG. The quality of evidence for migration was low however due to consistent reporting across studies. Administered dose was only reported in 1 (33%) study.

Adhesion barrier

While 4 (100%) human studies examining adhesion barriers had controlled groups, only 4 (44%) PEG barriers of interest were examined, and very few studies examined non-gynecological conditions. Additionally, sample size was small in 3 (75%) studies; 1 study only examined a PEG barrier (Intercoat) in 8 patients. Administered dose was only reported in 1 (25%) study. The quality of evidence was rated low for local responses since the quantity of evidence was limited, however most studies described either similar responses versus controls or did not attribute the responses to the PEG device. The quality of evidence for systemic responses was rated very low.

Vascular closure

7 human studies with controlled groups addressed 2 (40%) PEG vascular closure devices of interest. The quality of evidence was rated moderate for bleeding and hematoma due to consistent reporting of these outcomes from higher-quality studies with large enrollment and agreement with other PEG devices (e.g., aneurysm sealant, mesh). The quality of evidence was rated low for all other local responses, and very low for systemic responses (no studies investigating). Administered dose not reported in any study.

Mesh

4 human studies (some with control groups) examined 3 (23%) devices of interest. Enrollment was limited to only 314 patients overall. The quality of evidence was rated very low for local responses and systemic responses (no studies investigated). Administered dose was not reported in any study.

Embolic agent

2 single-arm studies examined LifePearl microspheres, 1 of 2 devices of interest. Studies examined mostly males aged over 55 years; overall enrollment only 117 patients. The quality of evidence was rated very low for local and systemic responses. Administered dose was reported in 2 (100%) studies.

Wound dressing

2 nonrandomized comparative studies examined Hemopatch in only 112 patients (mostly middle-aged females). No information was included on 5 other PEG-wound dressings, and limited evidence was identified for non-PEG dressings. Followup was limited to 6 months. The quality of evidence was rated very low for all responses; no studies investigated systemic responses. Administered dose was not reported in any study.

Bone filler/grafting

2 RCTs examined 1 (MembraGel) of 9 bone filler/grafts of interest. In addition, only maxilla/mandible defects were examined. The quality of evidence was rated very low for all responses; no studies investigated systemic responses. Administered dose was not reported in any study.

Dermal filler

There were no studies that met inclusion criteria for PEG dermal filler devices indicating an area of future research.

Hydrogel spacer

6 human studies addressed 1 prostate-rectal spacer of interest. The quality of evidence was low for local responses and systemic responses. 1 SR reporting data from the MAUDE database identified 25 total patients with AEs relating to SpaceOAR placement but prior to radiation. Systemic responses included pulmonary embolism, severe anaphylactic reaction, and severe urosepsis. In addition, 2 deaths (1 postprocedure) were reported, but an unclear association with the device was reported. Administered dose was not reported in any study.

Hydrogel tissue marker

There were no studies that met inclusion criteria for PEG hydrogel tissue marker devices indicating an area of future research.

Eye surgery dye

1 nonrandomized comparative study examined 2 eye surgery dyes of interest. The quality of evidence was rated very low for local and systemic responses. Administered dose was reported in 1 (100%) study.

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

Inclusion Criteria

1	**English language publication**
2	Published between January 2011 and April 2021
3	Human and animal studies
4	Systematic reviews, randomized controlled trials, cohort studies, case-control studies, cross-sectional studies, case series
5	Studies that evaluate toxicity/biocompatibility of PEG or priority devices that include this material

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.
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.

Literature Search for Polyethylene glycol (PEG)

Set Number	Concept	Search Statement
1.	PEG	'macrogol'/exp OR 'macrogol'/syn OR 'poly ethylene glycol*' OR 'polyethylene glycol*' OR 'hydra peg' OR 'polyethylene oxide' OR 'polyoxyethylene' OR 'poly oxyethylene' OR 'poly ethylene oxide' OR (peg NEAR/3 (based OR blend OR material OR hydrogel*))
2.	PEG Trade Names	pluronic* OR kolliphor* OR synperonic* OR poloxalene* OR poloxamer*
3.	PEG Devices: EMTREE index terms	'adhesion barrier'/exp OR 'anastomotic device'/exp OR 'balloon'/exp OR 'bandages and dressings':de OR 'blood patch'/exp OR 'bone graft'/exp OR 'catheter'/exp OR 'device material'/exp OR 'digestive prosthesis and implant'/exp OR 'dural substitute'/exp OR 'gynecological and obstetric prosthesis and implant'/exp OR 'hydrogel organ spacer'/exp OR 'implant'/exp OR 'implantable clip'/exp OR 'implantable drug delivery system'/exp OR 'injectable dermal implant'/exp OR 'medical device'/exp/mj OR 'neurological prosthesis and implant'/exp OR 'ophthalmic drug delivery device'/exp OR 'ophthalmological prosthesis and implant'/exp OR 'orthopedic prostheses, orthoses and implants'/exp OR 'otorhinolaryngology prosthesis and implant'/exp OR 'prostheses and orthoses'/exp OR 'sealant'/exp OR 'surgical glue'/exp OR 'spacer balloon'/exp OR 'surgical mesh'/exp OR 'tissue

Set Number	Concept	Search Statement
		adhesive'/exp OR 'tissue scaffold'/exp OR 'vascular closure device'/exp OR 'vessel sealing system'/exp OR 'wound dressing'/exp
4.	PEG Devices: Free-text terms	adhesive?:ti,ab OR 'anti adhesion?':ti,ab OR 'self-adhering':ti,ab OR 'adhering':ti,ab OR barrier?:ti,ab OR dressing?:ti,ab OR implant*:ti,ab OR 'mesh':ti,ab OR patch*:ti,ab OR sealant?:ti,ab OR 'spacer*':ti,ab OR (bone NEAR/2 (paste? OR filler? OR putty)):ti,ab
5.	Combine sets	(#1 OR #2) AND (#3 OR #4)
6.	PEG Devices: Product names	'actamax':ti,ab,kw,dn OR 'adherus':ti,ab,kw,dn OR 'autospray':ti,ab,kw,dn OR 'adhesix':ti,ab,kw,dn OR 'coseal':ti,ab,kw,dn OR 'duraseal':ti,ab,kw,dn OR 'elutibone':ti,ab,kw,dn OR 'ep granules':ti,ab,kw,dn OR 'focalseal*':ti,ab,kw,dn OR 'focalseall':ti,ab,kw,dn OR 'gelrinc':ti,ab,kw,dn OR 'gelrin c':ti,ab,kw,dn OR 'hemopatch':ti,ab,kw,dn OR 'hydropearl*':ti,ab,kw,dn OR 'lifepearl*':ti,ab,kw,dn OR 'ilm-blue':ti,ab,kw,dn OR 'matrix vsg':ti,ab,kw,dn OR 'matrixvsg':ti,ab,kw,dn OR 'membraneblue*':ti,ab,kw,dn OR 'mynx':ti,ab,kw,dn OR 'mynx cadence*':ti,ab,kw,dn OR 'mynxcadence*':ti,ab,kw,dn OR 'mynx grip*':ti,ab,kw,dn OR 'mynxgrip*':ti,ab,kw,dn OR 'nellix':ti,ab,kw,dn OR 'next science wound gel':ti,ab,kw,dn OR 'novabone':ti,ab,kw,dn OR 'ocuseal':ti,ab,kw,dn OR 'oxiplex*':ti,ab,kw,dn OR 'oxiplex sp':ti,ab,kw,dn OR 'medishield':ti,ab,kw,dn OR 'intercoat':ti,ab,kw,dn OR 'interpose':ti,ab,kw,dn OR 'dynavisc':ti,ab,kw,dn OR 'perfix light':ti,ab,kw,dn OR 'phasix st':ti,ab,kw,dn OR 'pleuraseal':ti,ab,kw,dn OR 'premvia':ti,ab,kw,dn OR 'prevadh':ti,ab,kw,dn OR 'progel':ti,ab,kw,dn OR 'repel-cv*':ti,ab,kw,dn OR 'repelcv*':ti,ab,kw,dn OR 'resure sealant':ti,ab,kw,dn OR 'sebacia*':ti,ab,kw,dn OR 'sepramesh':ti,ab,kw,dn OR 'signify bioactive':ti,ab,kw,dn OR 'skaffold nmx':ti,ab,kw,dn OR 'skaffoldnmx':ti,ab,kw,dn OR 'spaceoar*':ti,ab,kw,dn OR 'space oar*':ti,ab,kw,dn OR 'spraygel*':ti,ab,kw,dn OR 'spray gel*':ti,ab,kw,dn OR 'spray shield':ti,ab,kw,dn OR 'sprayshield':ti,ab,kw,dn OR 'straumann membragel':ti,ab,kw,dn OR 'sylys':ti,ab,kw,dn OR 'tridyne':ti,ab,kw,dn OR 'tridynevs':ti,ab,kw,dn OR 'uni-fuze-p':ti,ab,kw,dn OR 'ventralex st':ti,ab,kw,dn OR 'ventralight st':ti,ab,kw,dn OR 'ventrio st':ti,ab,kw,dn OR ((parietene OR parietex) NEAR/2 composite) OR 'synthemed*' OR 'remake':dn OR resure:dn OR 'elute':ff
7.	Combine and Limit by language and publication date	(#5 OR #6) AND [english]/lim AND [2011-2021]/py
8.	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

9.		'biocompatibility'/de OR biocompat* OR tribolog* OR 'bio compat*' OR 'biological* compat*' OR 'biological* evaluation'
10.		'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
11.		Leachable* OR extractable*
12.		(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 (implant* OR prosthes* OR prosthetic* OR spacer? OR patch? OR plug? OR plate? OR filler? OR device? OR mesh)
13.		'mechanics'/exp
14.		'device material'/exp/mj
15.		'Biomedical and dental materials'/exp/mj
16.	Combine sets	#9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15
17.	**PEG + Material Response**	**#8 AND #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*:ti,ab
23.		'foreign body' OR granuloma* OR 'foreign body'/exp OR 'macrophage'/exp OR 'macrophage*':ti,ab
24.		'adhesion'/exp OR 'tissue adhesion'/exp OR 'tissue response' OR 'tissue reaction' OR 'necrosis'/exp OR necrosis
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

28.	Combine sets **PEG + Material Response+ Host Response**	#17 AND #27
29.	**PEG devices + Host response**	#8 AND #27
30.	**Combine sets**	#28 OR #29
31.	**PEG systematic reviews**	#8 AND ('systematic review'/de OR 'meta analysis'/de OR ((meta NEAR/2 analy*):ti) OR 'systematic review':ti)
32.	**Final set**	**#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

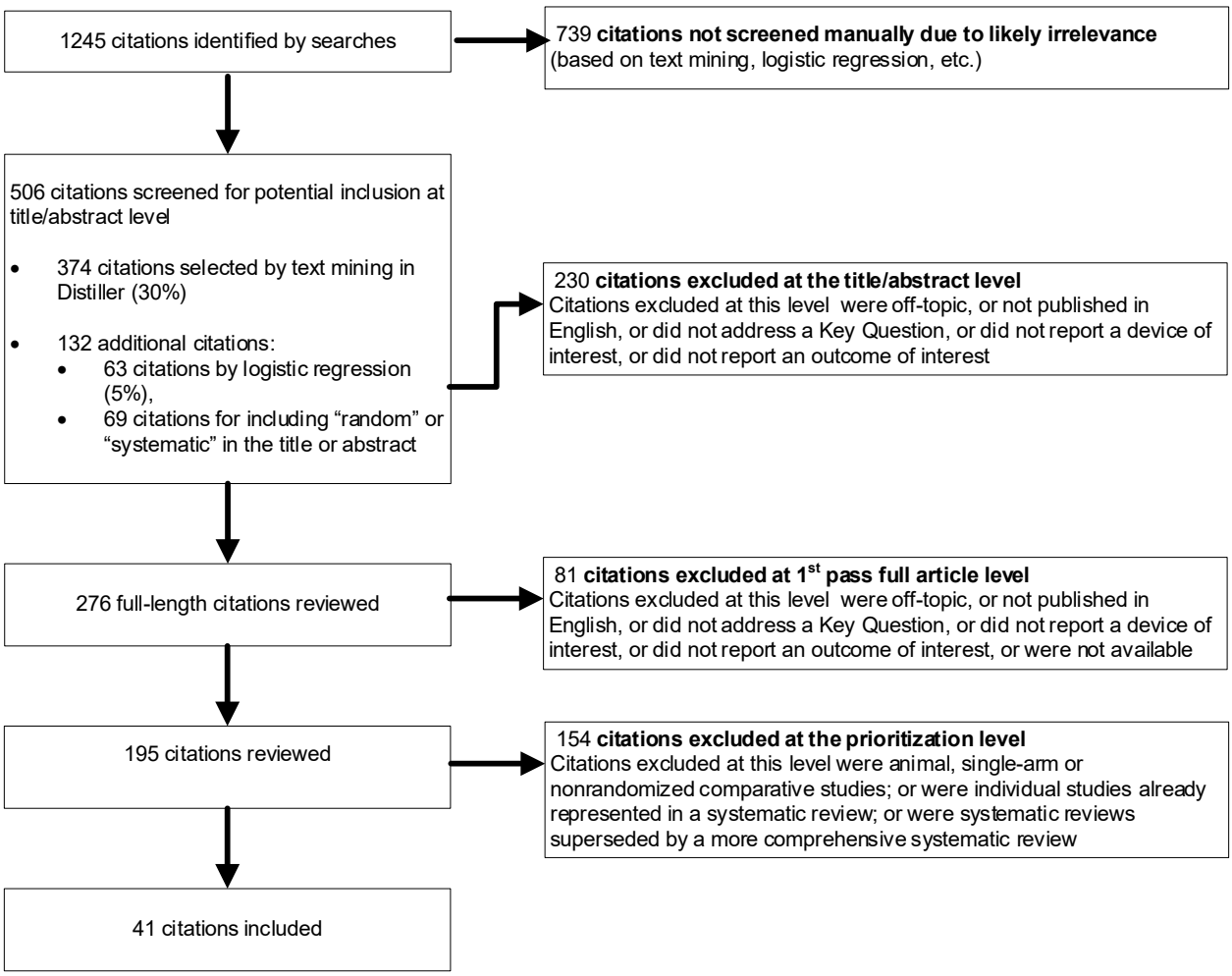
                - Emaciation
            - Body weight control
            - Fetus weight
            - Ideal body weight
            - Lean body weight
            - Live weight gain
        - Dry weight
        - Fresh weight
        - Molecular weight
        - Organ weight
            - Brain weight
            - 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



Appendix D. Evidence Tables

Table 7: PEG as a Material - Health Effects (In Vivo) Animal Studies

Source citation: Rashid et al. 2018[2]

Study Design: Nonrandomized comparative.

Device or Material: 5% PEG 4000 vs. 0.9% NaCl with/without BAM.

Route: Abdomen.

Dose: 5 ml 5% PEG or 0.9% NaCL; 2 cm x 2 cm defect.

Frequency/ Duration: Single administration.

Response: Inflammatory reaction containing lymphocytes and macrophages. Fibrosis.

Species (strain): Rats (Wistar albino).

Gender: Female.

Number per group: 8 (32 overall). Group 1 (control): PP mesh and 5 ml I.P. 0.9% NaCl. Group 2: PP mesh and 5 ml I.P. 5% PEG 4000 as adhesion barrier. Group 3: PP mesh covered with BAM and 5 ml I.P. 0.9% NaCl. Group 4: PP mesh covered with BAM and 5 ml I.P. PEG 4000 as adhesion barrier.

Observed adverse effects: Results for macroscopic (adhesion severity grade), and microscopic evaluations (fibrosis and inflammation) revealed 5% PEG 4000 plus BAM was significantly better vs. control in preventing complications. No significant differences were reported for Group 2 vs Group 3 or either group vs. control.

Macroscopic findings: Inflammatory reaction (containing lymphocytes and macrophages) was present in 3 cases (2 in Group 1 and 1 in Group 2). Highest adhesion percentage was noted in Group 1, lowest in Group 4 (PEG plus BAM)(e.g., Group 1 had 50% Grade 4 vs. Group 4 with 50% Grade 0). Small bowel obstruction, shrinkage and dislocation of PP mesh, and abscess formation were not observed.

Microscopic findings: Group 4 (PEG plus BAM): very small number of inflammatory cell infiltration and fibrosis (3 Grade 0, 3 Grade 1, 2 Grade 2 for fibrosis and inflammatory changes).Group 2 (PEG): normal lymphohistiocytic infiltration and vascularization (1 Grades 0 and 1, 4 Grade 2, and 2 Grade 3 for fibrosis and inflammatory changes). Group 1 (NaCl): fibrous adhesions and foreign body giant cell and fibrosis (2 Grades 1 and 2 each, 4 Grade 3 for fibrosis and inflammatory changes). Group 3 (NaCl and BAM): medium inflammatory cell infiltration and fibrosis (2 Grade 0 and 1 each, 3 Grade 2, 1 Grade 3 for fibrosis and inflammatory changes).

Timing of adverse effects: Up to 21 days.

Factors that predict response: NR.

Source citation: Thoma et al. 2012[1]

Study Design: RCT

Device or Material: PEG membrane plus DBBM (Institut Straumann AG), PGA-TMC plus DBBM, DBBM alone, control with defects untreated

Route: Mid-crestal incision from 2nd molar to the canine.

Dose: 10 mm length, 5 mm width, 6 mm depth defect; 120 mg of DBBM granules.

Frequency/ Duration: Single administration.

Response: Hemorrhage, Membrane detachment, Dissemination of DBBM granules.

Species (strain): Dog (hound-type).

Gender: Female.

Number per group: 18. 4 dogs were sacrificed immediately after surgery 2 (baseline), 7 dogs were sacrificed at 4 weeks, and 7 dogs were sacrificed at 16 weeks.

Observed adverse effects: After surgery 2 (baseline), 1 (25%) dog showed swelling in all 4 sites, with a severe hemorrhage at 1 site (unspecified). Swelling was possibly due to the early loss of the DBBM. Additional complications included marked signs of hemorrhage (2/7 (28.5%) PEG sites, 1/7 (14.2%) PGA-TMC site), membrane detachment (2/7 (28.5%) in PEG and PGA-TMC sites each) and dissemination of DBBM granules across all DBBM-filled sites. No complications were observed at 4 or 16 weeks.

Timing of adverse effects: Postoperatively.

Factors that predict response: NR.

Systemic Response/ Toxicity.

Source citation: Thoma et al. 2012[1]

Study Design: RCT

Device or Material: PEG plus DBBM, PGA-TMC, DBBM alone, control with defects untreated

Route: Mid-crestal incision from 2nd molar to the canine

Dose: 4 semi-saddle type ridge defects (10 mm length, 5 mm width, 6 mm depth)

Frequency/ Duration: Single administration.

Response: None reported

Species (strain): Dog (hound-type).

Gender: Female.

Number per group: 14.

Observed adverse effects: No systemic complications were observed.

Timing of adverse effects: N/A.

Factors that predict response: N/A.

BAM: bovine amniotic membrane; DBBM: deproteinized bovine bone mineral; IP: intraperitoneal; N/A: not applicable; NaCl: sodium chloride; PEG: polyethylene glycol; PGA-TMC: a resorbable glycolide trimethylene carbonate membrane plus DBBM; PP: polypropylene; RCT: randomized controlled trial

Table 8: Sealants - Health Effect (In Vivo) Human Studies

Source citation: Tan et al. 2020[3]

Study Design: Systematic review

Device Material: ReSure, Ocular Therapeutix, Inc. (vs. self-sealing; vs. bovine collagen; vs. Nylon suture); OcuSeal, BD Medical (vs. Nylon suture or stromal hydration; vs. self-sealing)

Contact Duration: Immediate to 14 days

Dose: Corneal Incision - ReSure: 2.2mm-3.5mm, OcuSeal: 2.8mm.

Frequency/ Duration: Single administration

Response: Foreign body sensation, High IOP, Leaking after re-provocation, Pain, SIA.

Patient characteristics (gender, mean age): NR.

Number per group: ReSure (n=23 to 295); OcuSeal (n=15 to 30).

Observed adverse effects: Higher immediate post-operative IOP using ReSure compared to self-sealing. Higher pain score for ReSure (1.3 vs. 1.1) compared to collagen corneal shield. After treatment, re-provocation with 1-oz. force resulted in 12 of 295 (4.1%) ReSure eyes leaking compared to 60 of 176 (34.1%) 11-0 Nylon sutured eyes. OcuSeal had lower SIA (0.6D vs. 1.3D) compared to 10-0 Nylon suture closure. OcuSeal had less foreign body sensation compared to sutured and stromal hydration groups over 14 days. No statistical difference in IOP between OcuSeal and self-sealed incisions immediate postoperative.

Timing of adverse effects: Immediate postoperative.

Factors that predict response: NR.

Source citation: Vaggers et al. 2020[4]

Study Design: Systematic review

Device Material: DuraSeal ([PEG] Integra LifeSciences) vs. SpaceOAR ([PEG] Boston Scientific, Augmenix)

Contact Duration: Median follow up time range 6 to 60 months

Dose: NR

Frequency/ Duration: NR

Response: Diarrhea, Fistula, Grade 1 Complications, Grade 2 Complications, Grade 3 Complications, Grade 4 Complications, Proctitis, Sensation of pressure in the rectum, Sudden need for defecation.

Patient characteristics (gender, mean age): NR.

Number per group: DuraSeal: 3 single arm studies: 347 total patients; 1 nonrandomized comparative study: 100 patients with DuraSeal vs. 100 patients without DuraSeal. SpaceOAR: 5 nonrandomized comparative studies: 254 with SpaceOAR, 502 without SpaceOAR

Observed adverse effects: DuraSeal: Acute GI toxicity was rare in two smaller single arm studies. One study (11 patients) reporting 0% grade 1 complications, and 9% grade 2 toxicity (fistula). One study (10 patients) reporting sensation of pressure in the rectum, and sudden need to defecate in 1 patient each. In a large cohort with over 300 patients, acute toxicity events were more common with 37.4% reporting Grade 1 complications and 2.8% reporting Grade 2 complications (mostly diarrhea). Late GI toxicity was more common with one small study (11 patients) having 36% Grade 1 or 2 complications, and 9% having Grade 3 or 4 complications. 1 patient had a prostatorectal fistula requiring a diverting colostomy. The large cohort study had 12.7% Grade 1 complications, 1.4% Grade 2 complications, 0.7% Grade 3 complications (including 1 case of severe proctitis, and 1 case of a fistula requiring colostomy). No complications were reported in the nonrandomized comparative study. SpaceOAR: See Table 10 for results.

Timing of adverse effects: Up to 6 or 60 months.

Factors that predict response: NR.

Source citation: Gologorsky et al. 2019[10]

Study Design: Nonrandomized comparative

Device Material: ProGel ([PEG] CR Bard Inc.) (vs. standard closure without Progel)

Contact Duration: 90 minutes

Dose: As indicated

Frequency/ Duration: Single administration

Response: Pneumothorax

Patient characteristics (gender, mean age): 50% female, 18 to 80 years (median 65 years).

Number per group: Progel (n=84); non-Progel (control, n=92)

Observed adverse effects: No statistically significant difference between patients who did or did not receive Progel. Thirty-four patients in each group had a pneumothorax visible on chest radiography within 90 minutes of surgery completion

Timing of adverse effects: 90 minutes postoperative

Factors that predict response: NR.

Source citation: Khoynezhad et al. 20185

Study Design: RCT

Device Material: Tridyne ([PEG] Neomend Inc.) vs. Gelfoam Plus ([non-PEG] Baxter Healthcare Corp)

Contact Duration: 30 days

Dose: ≤30 mL Tridyne per patient

Frequency/ Duration: Single or double administration

Response: Pericardial effusion

Patient characteristics (gender, mean age): 30.1% female, 20 to 89 years (median 64 years).

Number per group: Tridyne (n=106); Gelfoam Plus (n=50).

Observed adverse effects: One patient in the Tridyne group exhibited pericardial effusion. One patient each in the Gelfoam Plus group exhibited hematoma and hypotension; no patients with these symptoms in the Tridyne group

Timing of adverse effects: Through 30 days postoperative

Factors that predict response: NR

Source citation: Tew et al. 20179

Study Design: RCT

Device Material: DuraSeal ([PEG] Integra LifeSciences) vs. Adherus ([PEG] HyperBranch Medical Technology)

Contact Duration: 120 days

Dose: NR

Frequency/ Duration: Single or double administration

Response: Hematoma, Pseudomeningocele, Thrombosis

Patient characteristics (gender, mean age): Adherus (66.9% female, 51.2 years); DuraSeal (68.3% female, 49.6 years).

Number per group: Adherus (n=124); DuraSeal (control, n=126).

Observed adverse effects: No unanticipated SAEs occurred due to either of the hydrogel sealants. SAEs in each treatment group were typically mild or moderate and over half had resolved by the 120 day follow-up. Eight SAEs occurred in the Adherus group including extradural hematoma (n=1), and pseudomeningocele (n=3); aside from pseudomeningocele, these SAEs did not occur in the DuraSeal group. Two SAEs occurred in the DuraSeal group defined as intracranial venous sinus thrombosis (n=1) and pseudomeningocele (n=1); aside from pseudomeningocele, these SAEs did not occur in the Adherus group.

Timing of adverse effects: 50% of SAEs resolved by 120-day follow-up. In the Adherus group, median time to pseudomeningocele was 111 days postindex procedure (range 27-128 days). In the DuraSeal group, median time to pseudomeningocele was 8 days postindex procedure (range 1-111 days).

Factors that predict response: NR.

Source citation: Trew et al. 20178

Study Design: RCT

Device Material: Actamax Adhesion Barrier ([PEG] Actamax Surgical Materials LLC) vs. closure without Actamax

Contact Duration: 4 to 12 weeks

Dose: ≤30 mL Actamax per patient (11.3±4.3 mL)

Frequency/ Duration: Single or double administration

Response: Drug hypersensitivity, Dysmenorrhea, metrorrhagia, Ovarian cyst, Pain, Uterine disorder

Patient characteristics (gender, mean age): 100% female, 33.6 years

Number per group: Premenopausal women wishing to maintain fertility undergoing gynecologic laparoscopic abdominopelvic surgery with planned SLL. Actamax (n=35); control, surgery only (n=31).

Observed adverse effects:
Abdominal pain: 1 (2.9%) Actamax, 1 (3.2%) control.
Drug hypersensitivity: 1 (2.9%) Actamax, 0 (0.0%) control.
Dysmenorrhea/metrorrhagia: 1 (2.9%) Actamax, 0 (0.0%) control.
Ovarian cyst: 1 (2.9%) Actamax, 1 (3.2%) control.
Uterine disorder: 1 (2.9%) Actamax, 0 (0.0%) control.

Pain was assessed as "greater than expected" for one control subject at hospital discharge, and for three subjects (two Actamax, one control) at SLL

Timing of adverse effects: Discharge; SLL at 4 to 12 weeks

Factors that predict response: NR.

Source citation: Wright et al. 20156

Study Design: RCT

Device Material: DuraSeal Exact ([PEG] Integra LifeSciences) vs. standard closure methods

Contact Duration: 90 days

Dose: NR

Frequency/ Duration: Single or double administration

Response: CSF leak (reported as safety outcome), Neurological complications

Patient characteristics (gender, mean age): DuraSeal (59.5% female, 44.3±13.1 years); Control (62.5% female, 44.7±11.4 years).

Number per group: Subjects undergoing spinal surgery. DuraSeal (n=74); Control (n=24).

Observed adverse effects: CSF leakage was reported as a primary efficacy outcome and safety endpoint. Safety outcomes as follows:
8 CSF events in the DuraSeal group (11.0%) compared with 3 events (12.5%) in the control group. Of the 8 DuraSeal and 3 control subjects with CSF, 7 and 1, respectively, were Chiari patients with no significant differences in the 90-day CSF leak rate among them. Of the 30.4% CSF leaks in Chiari patients, 8.7% (2) were CSF fistula, 8.7% (2) were pseudomeningocele (surgical intervention required), and 13% (3) were pseudomeningocele (no surgical intervention required). There were 17 (23.3%) and 5 (20.8%) subjects with at least one SAE in the DuraSeal and control groups, respectively. The rates of serious neurological complications were comparable between groups (6.8% and 8.3%, respectively). There were no deaths, confirmed device-related adverse events, or unanticipated adverse device effects

Timing of adverse effects: Within 90 days.

Factors that predict response: Chiari malformation patients have an increased risk of complications

Source citation: Zhou et al. 201411

Study Design: Single arm

Device Material: DuraSeal ([PEG] Covidien)

Contact Duration: 90 day post-op clinical follow-up

Dose: NR

Frequency/ Duration: Single administration

Response: Meningitis

Patient characteristics (gender, mean age): 43.6% female, 10.2±4.3 years.

Number per group: 163 pediatric patients with PEG sealant as an adjunct to standard sutured dural closure techniques

Observed adverse effects: 4 patients (2.4%) required revision surgery; 1 patient developed postoperative meningitis (0.6%). There were no deaths or neurological deficits within 90-day follow-up time period.

Timing of adverse effects: NR.

Factors that predict response: Treatment with a nonautologous graft or no graft

Source citation: De Leyn et al. 20117

Study Design: RCT

Device Material: PleuraSeal ([PEG] Covidien) vs. standard lung closure

Contact Duration: 30 days

Dose: NR

Frequency/ Duration: Single administration

Response: Bronchopleural fistula, Emphysema, Hydropneumothorax, Respiratory distress, Pain, Pleural effusion, Pneumothorax

Patient characteristics (gender, mean age): PleuraSeal (41.9% female, 61.5 years); Control (37.3% female, 62.8 years).

Number per group: Covidien (n=62); Control (n=59).

Observed adverse effects: The incidence of predefined complications or SAEs was similar between the DuraSeal and control groups (35.5% vs. 23.7%). There were no deaths.
Acute respiratory distress syndrome: 1 (1.6%) PleuraSeal, 0 (0.0%) control.
Atelectasis: 0 (0.0%) PleuraSeal, 1 (1.7%) control.
Bronchopleural fistula: 1 (1.6%) PleuraSeal, 0 (0.0%) control.
Pulmonary embolism: 0 (0.0%) PleuraSeal, 1 (1.7%) control.
Emphysema: 1 (1.6%) PleuraSeal, 0 (0.0%) control.
Pain: 2 (3.2%) PleuraSeal, 0 (0.0%) control.
Pleural effusion: 1 (1.6%) PleuraSeal, 0 (0.0%) control.
Pneumothorax: 5 (8.1%) PleuraSeal, 1 (1.7%) control.
Hydropneumothorax: 1 (1.6%) PleuraSeal, 2 (3.4%) control

Timing of adverse effects: Within 30 day follow-up

Factors that predict response: NR.

Source citation: Khoynezhad et al. 2018[5]

Study Design: RCT

Device Material: Tridyne ([PEG] Neomend Inc.) vs. Gelfoam Plus ([non-PEG] Baxter Healthcare Corp)

Contact Duration: 30 days

Dose: ≤30 mL Tridyne per patient

Frequency/ Duration: Single or double administration

Response: Azotemia, Stroke

Patient characteristics (gender, mean age): 30.1% female, 20 to 89 years (median 64 years)

Number per group: Tridyne (n=106); Gelfoam Plus (n=50)

Observed adverse effects: Two patients each in the Tridyne and Gelfoam Plus groups exhibited stroke. One patient (0.9%) in the Tridyne group exhibited azotemia compared to 0 patients in the GelFoam group

Timing of adverse effects: Through 30 days postoperative

Factors that predict response: NR.

Source citation: Tew et al. 2017[9]

Study Design: RCT

Device Material: DuraSeal ([PEG] Integra LifeSciences) vs. Adherus ([PEG] HyperBranch Medical Technology)

Contact Duration: 120 days

Dose: NR

Frequency/ Duration: Single or double administration

Response: Convulsion, Dysphagia, Headache, Respiratory failure

Patient characteristics (gender, mean age): Adherus (66.9% female, 51.2 years); DuraSeal (68.3% female, 49.6 years).

Number per group: Adherus (n=124); DuraSeal (control, n=126).

Observed adverse effects: No unanticipated SAEs occurred due to either of the hydrogel sealants. SAEs in each treatment group were typically mild or moderate and over half had resolved by the 120-day follow-up. Eight SAEs occurred in the Adherus group (but not the DuraSeal group) including convulsion (n=1), dysphagia (n=1), headache (n=1), and respiratory failure (n=1).

Timing of adverse effects: 50% of SAEs resolved by 120-day follow-up.

Factors that predict response: NR.

Source citation: Trew et al. 2017[8]

Study Design: RCT

Device Material: Actamax Adhesion Barrier ([PEG] Actamax Surgical Materials LLC) vs. closure without Actamax

Contact Duration: 4 to 12 weeks

Dose: ≤30 mL Actamax per patient (11.3±4.3 mL)

Frequency/ Duration: Single or double administration

Response: Headache, Hypersensitivity, Paresthesia, Rash

Patient characteristics (gender, mean age): 100% female, 33.6 years.

Number per group: Premenopausal women wishing to maintain fertility undergoing gynecologic laparoscopic abdominopelvic surgery with planned SLL. Actamax (n=35); control, surgery only (n=31).

Observed adverse effects:
Headache: 2 (5.7%) Actamax, 2 (6.5%) control.
Parasthesia: 1 (2.9%) Actamax, 0 (0.0%) control.
Hypersensitivity: 1 (2.9%) Actamax, 1 (3.2%) control.
Skin rash: 2 (5.7%) Actamax, 0 (0.0%) control.
Rash pruritic: 0 (0.0%) Actamax, 1 (3.2%) control.
Erythema and pruritus: 0 (0.0%) Actamax, 1 (3.2%) control.
Dizziness: 0 (0.0%) Actamax, 1 (3.2%) control.
Constipation: 0 (0.0%) Actamax, 1 (3.2%) control.
Vomiting: 0 (0.0%) Actamax, 1 (3.2%) control

Timing of adverse effects: Discharge; SLL at 4 to 12 weeks

Factors that predict response: NR.

Source citation: De Leyn et al. 2011[7]

Study Design: RCT

Device Material: PleuraSeal ([PEG] Covidien) vs. standard lung closure

Contact Duration: 30 days

Dose: NR

Frequency/ Duration: Single administration

Response: Cardiac failure, Stroke, Subcutaneous emphysema, Ventricular fibrillation

Patient characteristics (gender, mean age): PleuraSeal (41.9% female, 61.5 years); Control (37.3% female, 62.8 years).

Number per group: Covidien (n=62); Control (n=59).

Observed adverse effects: The incidence of predefined complications or SAEs was similar between the PleuraSeal and control groups (35.5% vs. 23.7%). There were no deaths.
Cardiac arrest: 0 (0.0%) PleuraSeal, 1 (1.7%) control.
Cardiac failure chronic: 1 (1.6%) PleuraSeal, 0 (0.0%) control.
Ischemic stroke: 1 (1.6%) PleuraSeal, 0 (0.0%) control.
Subcutaneous emphysema: 1 (1.6%) PleuraSeal, 0 (0.0%) control.
Peripheral ischemia: 0 (0.0%) PleuraSeal, 1 (1.7%) control.
Fatigue: 0 (0.0%) PleuraSeal, 2 (3.4%) control

Timing of adverse effects: Within 30 day follow-up

Factors that predict response: NR.

CSF: cerebrospinal fluid; IOP: intraocular pressure; NR: not reported; PEG: polyethylene glycol; RCT: randomized controlled trial; SAE: serious adverse event; SIA: surgically induced astigmatism; SLL: second-look laparoscopy

Table 9: Aneurysm sealant- Health Effect (In Vivo) Human Studies

Local Response/ Toxicity.

Source citation: Lareyre et al. 2020[12]

Study Design: Systematic review

Device Material: Nellix EVAS ([PEG] Endologix, Inc.)

Contact Duration: 5 to 25 months

Dose: 7-56.7 mL

Frequency/ Duration: Single administration

Response: Endoleak, Hematoma, Pseudoaneurysm

Patient characteristics (gender, mean age): Gender NR, 70-87 years.

Number per group: 1 to 15 patients per study with prior EVAR who underwent EVAS. Of the 11 included studies (n=46), 7 were case reports

Observed adverse effects: The presence of new endoleaks was reported in five patients (9.8%) during the follow-up: four type II endoleaks and one type Ia endoleak. Complications required a re-intervention using an embolization procedure. One study reported a patient with postoperative hematoma and common femoral artery pseudoaneurysm, which thrombosed spontaneously. Three studies specifically reported no graft thrombosis or chimney graft occlusion

Timing of adverse effects: The type II endoleaks occurred at 5, 12, 14, and 26 months post-surgery. The type Ia endoleak was diagnosed at 5-month post-surgery

Factors that predict response: Prior EVAR.

Source citation: Choo et al. 2019[13]

Study Design: Systematic review

Device Material: Nellix EVAS ([PEG] Endologix, Inc.)

Contact Duration: 1 to 23 months

Dose: NR

Frequency/ Duration: Single administration

Response: Bleeding, Embolus, Endoleak, Enlargement, Hematoma, Migration, Occlusion, Rupture, Thrombus

Patient characteristics (gender, mean age): 11% female, 74±2 years.

Number per group: 5 to 335 patients with asymptomatic, non-ruptured AAA treated with EVAS reported in 14 single-arm studies (n=1510).

Observed adverse effects: Nine studies (n=902) reported data on postoperative complications ranging from 0 to 60% incidence rates. Complications included endoleak (2 studies), thrombus formation in the endograft (1 study), groin hematoma (3 studies), occlusion of the femoral or hypogastric artery (1 study each), embolus formation (1 study), and duodenal bleeding (1 study).

Aneurysm rupture within 30 days of procedure was reported in 8 studies, with an incidence rate of 0 to 2%. In 1 to 23 month follow-up, 12 studies reported 5 cases of ruptured AAA with an incidence rate of 0 to 1.3%.

49 of 1,510 patients had endoleak within 30 days of the procedure (Type I=59% endoleaks; remaining leaks were type II). Six studies found no endoleak during 1 to 23 months follow-up; 8 studies found 31 endoleaks (Type 1=22, Type II=8, Type III=1).

Five studies reported sac enlargement within 30 days; sac enlargement during 12 to 23 month follow-up incidence rate was 0 to 5%.

Five studies reported device migration occurring within 30 days of surgery with a rate ranging from 0 to 6.7%. During follow-up of 5 to 23 months, nine studies reported device migration with incidence rate from 0 to 13%.

Timing of adverse effects: 30 days to 23 months

Factors that predict response: NR.

Systemic Response/ Toxicity.

Source citation: Martinelli et al. 2020[14]

Study Design: Nonrandomized comparative

Device Material: Nellix EVAS ([PEG] Endologix, Inc.) vs. EVAR with ePTFE devices (non-PEG)

Contact Duration: 12 to 60 months

Dose: NR

Frequency/ Duration: Single administration

Response: Cardiac complications, Fever, High-sensitivity C-reactive protein elevation, Leukocytosis, PIS (systemic inflammation)

Patient characteristics (gender, mean age): 14% female, 73.7±7.5 years.

Number per group: EVAS with Nellix (n=58); EVAR with ePTFE ([Group A Gore Excluder, n=55], [Group B Endologix AFX, n=56]).

Observed adverse effects: 13.8% of EVAS patients exhibited PIS, compared to 38.7% in the EVAR group (p=0.001). Inflammatory markers of PIS included: 8.6% of patients in the EVAS group with fever greater than 38.5C versus 34.5% of patients in the EVAR group; 12.1% of patients with leukocytosis greater than 13,000 cells per mL versus 20.8% in the EVAR group; and 46.6% of patients in the EVAS group with high-sensitivity C-reactive protein elevation greater than 15 mg/L versus 72.7% in the EVAR group.
No significant new-onset of mural thrombus occurred following EVAS, compared to new-onset thrombus of 21% (Group A) and 14% (Group B).
Major adverse events were proportionally but not statistically significantly less frequent after EVAS (10.3%) than after EVAR (Group A=16.4%, Group B=8.9%).
15.5% of EVAS patients had cardiac complications versus 36.4% of patients in EVAR Group A and 41.1% in EVAR Group B. 44.8% of EVAS patients had non-cardiac major complications versus 36.4% of patients in EVAR Group A and 41.1% in EVAR Group B.

Timing of adverse effects: PIS response always occurred within the first 2 days after endografting. Other complications occurred during a mean follow-up period of 24 months (12 to 60 months).

Factors that predict response: NR

Source citation: Choo et al. 2019[13]

Study Design: Systematic review

Device Material: Nellix EVAS ([PEG] Endologix, Inc.)

Contact Duration: 1 to 23 months

Dose: NR

Frequency/ Duration: Single administration

Response: Death, Paraparesis, PIS, Respiratory failure, Stroke

Patient characteristics (gender, mean age): 11% female, 74±2 years.

Number per group: 5 to 335 patients with asymptomatic, non-ruptured AAA treated with EVAS reported in 14 single-arm studies (n=1510).

Observed adverse effects: Nine studies (n=902) reported data on postoperative complications ranging from 0 to 60% incidence rate. Complications included respiratory failure (3 studies), hemispheric stroke (1 study), PIS (five cases in 1 study), and paraparesis (1 study).
Thirteen studies reported mortality within 30 days of surgery with rates ranging from 0 to 4.8%. Seven out of 10 deaths occurring within 30 days were non-aneurysm/device related. Six of 67 deaths during follow-up were aneurysm-related.

Timing of adverse effects: 30 days to 23 months.

Factors that predict response: NR.

AAA: abdominal aortic aneurysm; ePTFE: expanded polytetrafluoroethylene; EVAR: endovascular aneurysm repair; EVAS: endovascular aneurysm sealing; mg: milligram; mL: milliliter; PEG: polyethylene glycol; PIS: postimplantation syndrome; NR: not reported

Table 10: Adhesion barrier - Health Effect (In Vivo) Human Studies

Source citation: Ten Broek et al. 2014[15]

Study Design: Systematic review

Device Material: SprayGel, SprayShield ([PEG] Confluent Surgical Inc.); Interceed ([non-PEG] J&J); Seprafilm ([non-PEG, Sanofi); Adept ([non-PEG], Baxter).
All vs. no barrier.

Contact Duration: NR

Dose: NR

Frequency/ Duration: NR

Response: SAEs (not defined)

Patient characteristics (gender, mean age):
SprayGel: 6/7 studies 100% female (gynecological), age NR; No gender/age reported for colorectal study.
Interceed: 12/12 studies 100% female, age NR.
Seprafilm: 1/10 studies 100% female (gynecological), age NR. No gender/age reported for colorectal, hepatic, gastric, or general pediatric studies.
Adept: 2/4 studies 100% female (gynecological), age NR. No gender/age reported for colorectal studies

Number per group:.
SprayGel: 11 to 72.
Interceed: 8 to 694.
Seprafilm: 54 to 1,791.
Adept: 23 to 498.

Observed adverse effects:
SprayGel: The incidence of SAEs did not differ in three trials of gynecological surgery (RR=0.55) and colorectal surgery (RR=1.11). The first study had 5 events and 6 events in the experimental and control groups, respectively. The second study had 0 SAEs reported for the experimental and control groups. The third study reported 6 SAEs in each the experimental and control groups. PEG significantly reduced adhesion scores in both gynecological surgery and in one trial of colorectal surgery.

Interceed: No evidence exists for a beneficial effect on the incidence of SAEs. Incidence of SAE after

myomectomy was much the same between two groups in one trial (RR 0.80). Postoperative fever was the only SAE recorded for both groups.

Seprafilm: 7 trials studied the incidence of SAEs, 5 for colorectal surgery and one each for hepatic and gastric. Differences between groups for the incidences of SAEs were all non-significant. In one trial, treatment wrapped around a new bowel anastomosis seemed to result in a higher incidence of SAEs including abscesses, fistulas, and anastomotic leakages.

Adept: No beneficial effects on the number of SAEs. There is evidence of a moderate risk for random error that the treatment reduces the incidence of small bowel obstruction. Incidence of SAEs was similar among the groups in gynecological surgery (RR 1.00) and lower alimentary tract surgery (RR 0.98).

Timing of adverse effects: NR

Factors that predict response: NR

Source citation: Rhyne et al. 2012[17]

Study Design: RCT

Device Material: Oxiplex ([PEG] FzioMed Inc.) vs. surgery-only

Contact Duration: 6 months

Dose: NR

Frequency/ Duration: Single administration

Response: No device-related responses

Patient characteristics (gender, mean age): Patients undergoing single-level lumbar discectomy. Oxiplex (50.85% female, 41.8 years); Control (44% female, 41.7 years

Number per group: Oxiplex (n=171); Control (surgery-only, n=168) available at 6 month follow-up

Observed adverse effects: No significant differences were found in adverse events between treatment and control groups. Investigators determined that no SAEs were due to gel use.

Back Pain: 44 (24.9%) Oxiplex, 39 (22.3%) control

Intervertebral disc protrusion: 4 (2.3%) Oxiplex, 9 (5.1%) control.

Timing of adverse effects: 6 months

Factors that predict response: NR.

Source citation: Di Spiezio et al. 2011[18]

Study Design: Nonrandomized comparative

Device Material: Intercoat ([PEG] Gynecare div Ethicon Inc.) vs. surgery-only

Contact Duration: 1 month

Dose: 10 mL

Frequency/ Duration: Single administration

Response: Worsening patency (obstruction)

Patient characteristics (gender, mean age): 100% female, premenopausal women diagnosed at office hysteroscopy as having single or multiple lesions suitable for surgical treatment or with resistant dysfunctional uterine bleeding requiring endometrial ablation

Number per group: Intercoat (n=55); Control (hysteroscopic surgery only, n=55).

Observed adverse effects: Improvement in patency of the internal uterine ostium at follow-up was significantly higher in the Intercoat group (23 of 55, 41.9%) than in the control group (3 of 55, 5.8%). Worsening of patency at follow-up was significantly higher in the control group (10 of 55, 18.2%) in comparison with the Intercoat group (1 of 55, 2.1%). No adverse gel-related effects were noted.

Timing of adverse effects: 1 month.

Factors that predict response: NR

Source citation: Banasiewicz et al. 2013[16]

Study Design: RCT

Device Material: SprayShield (PEG) vs. standard treatment

Contact Duration: 10 to 12 weeks

Dose: NR

Frequency/ Duration: Single Administration

Response: No device-related responses

Patient characteristics (gender, mean age): NR.

Number per group: SprayShield (n=8) to prevent abdominal adhesions; Control (no adhesion barrier, n=3).

Observed adverse effects: Five mild adverse events in all investigation centers including leukocytosis and hepatic enzyme increase. Two SAEs reported (dehydration, fasciitis). 50% of subjects in the SprayShield group and 33.3% in the control group experienced at least 1 adverse event. Differences in rates were not statistically significant. Investigators determined that all events had no relationship to the treatment

Timing of adverse effects: 10 to 12 weeks

Factors that predict response: NR.

Source citation: Rhyne et al. 2012[17]

Study Design: RCT

Device Material: Oxiplex ([PEG] FzioMed Inc.) vs. surgery-only

Contact Duration: 6 months

Dose: NR

Frequency/ Duration Single Administration:

Response: Arthralgia, Chills, Constipation, Dizziness, Fever, Headache, Hypoaesthesia, Hyporeflexia, Insomnia, Muscle spasm/weakness, Myalgia, Nausea, Pain, Pruritus, Sensory loss, Vomiting, Weakness

Patient characteristics (gender, mean age): Patients undergoing single-level lumbar discectomy. Oxiplex (50.85% female, 41.8 years); Control (44% female, 41.7 years).

Number per group: Oxiplex (n=171); Control (surgery-only, n=168) available at 6 month follow-up

Observed adverse effects: No significant differences were found in adverse events between treatment and control groups. Investigators determined that no SAEs were due to gel use.
Constipation: 12 (6.8%) Oxiplex, 6 (3.4%) control.
Nausea: 35 (19.8%) Oxiplex, 36 (20.6%) control.
Vomiting: 10 (5.6%) Oxiplex, 9 (5.1%) control.
Chills: 8 (4.5%) Oxiplex, 8 (4.6%) control.
Fever: 8 (4.5%) Oxiplex, 11 (6.3%) control.
Arthralgia: 12 (6.8%) Oxiplex, 12 (6.9%) control.
Buttock pain: 12 (6.8%) Oxiplex, 13 (7.4%) control.
Muscle spasm: 25 (14.1%) Oxiplex, 31 (17.7%) control.
Muscle weakness: 9 (5.1%) Oxiplex, 9 (5.1%) control.
Musculoskeletal stiffness: 9 (5.1%) Oxiplex, 5 (2.9%) control.
Myalgia: 6 (3.4%) Oxiplex, 13 (7.4%) control.
Pain in extremity: 26 (14.7%) Oxiplex, 38 (21.7%) control.
Dizziness: 10 (5.6%) Oxiplex, 8 (4.6%) control.
Headache: 14 (7.9%) Oxiplex, 12 (6.9%) control.
Hypoaesthesia: 18 (10.2%) Oxiplex, 26 (14.9%) control.
Hyporeflexia: 9 (5.1%) Oxiplex, 4 (2.3%) control.
Sensory loss: 4 (2.3%) Oxiplex, 8 (4.6%) control.
Insomnia: 12 (6.8%) Oxiplex, 7 (4.0%) control.
Pruritis: 8 (4.5%) Oxiplex, 6 (3.4%) control

Timing of adverse effects: 6 months.

Factors that predict response: NR.

ml: milliliters; NR: not reported; PEG: polyethylene glycol; RCT: randomized controlled trial; SAE: serious adverse event

Table 11: Vascular closure - Health Effect (In Vivo) Human Studies

Source citation: Kennedy et al. 2021[20]

Study Design: Systematic review

Device Material: PEG Devices (Mynx, MynxGrip; AccessClosure Inc.) vs. 6 non-PEG Devices (Angioseal, Exoseal, Femoseal, Glubran 2, Perclose, Starclose)

Contact Duration: NR

Dose: NR

Frequency/ Duration: Single antegrade intervention originating at the common femoral artery (CFA) or the superior femoral artery (SFA)

Response: Bleeding complications (bleeding/hematoma, retroperitoneal bleed). Overall complications (vessel occlusion or stenosis, embolization, pseudoaneurysm formation, anteriovenous fistular formation, and bleeding-related complications).

Patient characteristics (gender, mean age): NR.

Number per group:
CFA Approach
Mynx/MynxGrip (2 studies, n=108); Angioseal-CFA (10 studies, n=2559), Exoseal-CFA (4 studies, n=475), Femoseal-CFA (1 study, n=111), Glubran-CFA 2 (1 study, n=104), Starclose (4 studies, n=341)

SFA Approach
Angioseal (1 study, n=158), Exoseal (1 study, n=110), Perclose (1 study, n=23), Starclose (2 studies, n=135)

Observed adverse effects:

CFA Approach
PEG Devices:
Mynx: Overall Complications ES 0.92 (95% CI 0.00 to 4.18); Bleeding Complications ES 0.44 (95% CI 0.00 to 3.24)
Non-PEG Devices:
Angioseal: Overall Complications ES 3.81 (95% CI 0.93 to 7.93); Bleeding Complications ES 2.92 (95% CI 0.26 to 7.29)
Exoseal: Overall Complications ES 4.69 (95% CI 1.31 to 9.74); Bleeding Complications ES 3.05 (95% CI 0.91 to 6.16)
Femoseal: Overall Complications ES 7.21 (95% CI 3.70 to 13.58); Bleeding Complications ES 7.21 (95% CI 3.70 to 13.58)
Glubran 2: Overall Complications ES 3.85 (95% CI 1.51 to 9.47); Bleeding Complications ES 1.92 (95% CI 0.53 to 6.74)
Starclose: Overall Complications ES 7.43 (95% CI 4.71 to 10.62); Bleeding Complications ES 6.78 (95% CI 4.18 to 9.87)

SFA Approach
Non-PEG Devices:
Angioseal: Overall Complications ES 7.0 (95% CI 3.9 to 12.0); Bleeding Complications ES 6.3 (95% CI 3.5 to 11.3)
Exoseal: Overall Complications ES 3.6 (95% CI 1.4 to 9.0); Bleeding Complications ES 0.9 (95% CI 0.2 to 5.0)
Perclose: Overall Complications ES 0.0 (95% CI 0.0 to 14.3); Bleeding Complications ES 0.0 (95% CI 0.0 to 14.3)
Starclose: Overall Complications ES 10.1 (95% CI 5.3 to 15.9); Bleeding Complications ES 6.4 (95% CI 2.6 to 11.4)

Timing of adverse effects: NR

Factors that predict response: NR

Source citation: Ben-Dor et al. 2018[21]

Study Design: RCT

Device Material: 1 PEG Device (MynxGrip, AccessClosure, Inc.) vs.Manual Compresion

Contact Duration: NR

Dose: NR

Frequency/ Duration: Insertion into the common femoral vein via 5, 6, or 7 F sheath access

Response: None reported

Patient characteristics (gender, mean age): MynxGrip: 72.7 years (14.7), 41.3% female; Manual compression: 72.4 years (13.8), 46.2%.

Number per group: Mynxgrip: 103; Manual Compression: 104

Observed adverse effects: No complications in either group

Timing of adverse effects: Up to discharge (length of stay NR).

Factors that predict response: nr

Source citation: Jones et al. 2018[23]

Study Design: Nonrandomized comparative

Device Material: 1 PEG Device (Mynx Grip, (Cardinal Health) vs. 4 non-PEG devices (AngioSeal, ExoSeal, Perclose, StarClose) vs. Manual Compression

Contact Duration: 30 days post-operation

Dose: NR

Frequency/ Duration: Insertion into the femoral vein via 6 F sheath access

Response: Bleeding (major or minor), Extended recovery, Hematoma (major and minor), Retroperitoneal bleed.

Patient characteristics (gender, mean age): 66 years (SD 13.26), 52.21% female.

Number per group:
PEG Devices: Mynx: 598;
Non-PEG Devices: AngioSeal: 231, ExoSeal: 210, Perclose: 455, Starclose: 316, Manual Compression: 88

Observed adverse effects: Minor complications (53 overall) included hematoma, bleeding, hypotension, arterial dissection, or prolonged recovery (>2 hours) not requiring inpatient management.
Minor complication rates: 18 (5.7%) StarClose, 6 (2.9%) ExoSeal, 14 (2.3%) Mynx, 12 (2.6%) Perclose, 3 (1.3%) AngioSeal.
Major complications (11 overall) included hematoma, bleeding, retroperitoneal bleed, or thrombosis.
Major complication rates: 3 (1.3%) AngioSeal, 4 (0.7%) Mynx, 2 (0.6%) StarClose, 2 (0.4%) Perclose, 0 (0%) ExoSeal

PEG Devices:
Mynx: 6 minor hematoma, 5 extended recovery, 3 minor bleeding, 2 major hematoma, 1 major bleeding, 1 retroperitoneal bleed
Non-PEG Devices
AngioSeal: 2 minor hematoma, 1 extended recovery, 3 major hematoma
ExoSeal: 3 minor hematoma, 3 minor bleeding
Perclose: 7 minor hematoma, 2 extended recovery, 2 minor bleeding, 1 hypotension, 2 major hematomas
Starclose: 13 minor hematomas, 3 extended recovery, 1 minor bleeding, 1 hypotension, 1 major bleeding, 1 retroperitoneal bleed

Other
Manual Compression: 1 hematoma, 1 arterial dissection, 1 retriperitoneal bleed, 1 thrombosis

Timing of adverse effects: Up to 30 days post-operation

Factors that predict response: NR.

Source citation: Noori and Eldrup-Jorgensen 2018[19]

Study Design: Systematic review

Device Material: 1 PEG Device (MynxGrip, AccessClosure, Inc.) vs. 14 Non-PEG Devices (AngioSeal, Arstasis, Boomerang, Cardiva, Catalyst II, Exoseal, Ensure Medical VCD, FemoSeal, FISH, Perclose ProGlide, ProStar, ProStar XL, StarClose, Vascade)

Contact Duration: 30 days

Dose: NR

Frequency/ Duration: Single surgery

Response: Pain, Vascular complications

Patient characteristics (gender, mean age): NR.

Number per group:
PEG Devices: MynxGrip: 3 studies examining MynxGrip alone or against other devices with 745 enrolled patients.
Non-PEG Devices: 31 studies examining a listed non-PEG device alone or against other devices with 13,711 enrolled patients.

Observed adverse effects: In MynxGrip studies, 1 study comparing MynxGrip to AngioSeal found lower pain with MynxGrip. 1 single-arm study of MynxGrip found a low incidence of vascular complications, and one non-randomized comparative study found low incidence of vascular complications for MynxGrip that was comparable to other VCDs (Perclose and AngioSeal). Listed non-PEG studies generally had a low incidence of vascular complications.

Timing of adverse effects: Up to 30 days.

Factors that predict response: NR

Source citation: Elmasri et al. 2017[25]

Study Design: Nonrandomized comparative

Device Material: 1 PEG Device (Mynx, AccessClosure, Inc.) vs. 4 non-PEG devices (AngioSeal, FISH, Perclose, Starclose) vs. manual compression

Contact Duration: 30 days post-operation

Dose: NR

Frequency/ Duration: Single or bilateral insertion into common femoral artery; bilateral procedures treated as two separate data points

Response: Major complication rate (pseudoaneurysm, bleeding/hematoma, arterial stenosis). Total complication rate (also includes pain, serosanguinous discharge).

Patient characteristics (gender, mean age): 59.8 years (SD 1.09), between 43.4% and 46.8% male

Number per group:
PEG Devices: Mynx: 56;
Non-PEG Devices: AngioSeal: 478, FISH: 56, Perclose: 61, Starclose: 68, Manual Compression: 188

Observed adverse effects: Complications were categorized as minor and major (requiring therapy and <48 hours of hospitalization or major therapy and prolonged hospitalization).

14 major complications (11 pseudoaneurysms, 2 hematomas, 1 stenosis): 9 with Angio-Seal (1.9%), 3 with manual compression (1.6%), and 1 with Mynx (1.8%) and Starclose (1.5%); 0 with FISH or Perclose.

71 total complications (mostly minor bleeding or small hematomas): Angio-Seal (7.0%), FISH (1.8%), Mynx (14.5%), Perclose (6.6%), Starclose (1.5%), and manual compression (11.2%).

PEG Devices:
Mynx: total complication rate (minor and major complications): 14.5%, major complication rate 1.8%

Non-PEG Devices:
AngioSeal: total complication rate: 7%, major complication rate: 1.9%
FISH: total complication rate: 1.8%, major complication rate: 0%
Perclose: total complication rate: 6.6%, major complication rate: 0%
Starclose: total complication rate: 1.5%, major complication rate: 1.5%

Other:
Manual compression: total complication rate: 11.2%, major complication rate: 1.6%

Timing of adverse effects: Up to 1 month.

Factors that predict response: NR.

Source citation: Resnic et al. 2017[24]

Study Design: Nonrandomized comparative

Device Material: Mynx (AccessClosure, Inc.)

Contact Duration: 12 months

Dose: NR

Frequency/ Duration: Single administration

Response: Access-site bleeding, Post-procedural blood transfusion, Vascular complications.

Patient characteristics (gender, mean age):
Before Propensity Matching
Mynx: 65.3 years (SD 11.9), 34.3% female;
Alternative Device: 65.1 years (SD 12.1), 30.5% female

After Propensity Matching:
Mynx: 65.3 years (SD 11.9), 34.3% female;
Alternative Device: 65.3 years (SD 12.0), 34.2% female

Number per group:
Before Propensity Matching
73,164 Mynx; 603,437 with an alternative device

After Propensity Matching:
73,124 Mynx; 73,214 matched cohort with an alternative device

Observed adverse effects:
After Propensity Matching: Mynx: 277 access-site bleeding (0.4%), 1,328 blood transfusion (1.8%), 883 vascular complications (1.2%). Other Device: 207 access-site bleeding (0.3%), 1,080 blood transfusion (1.5%), 555 vascular complications (0.8%)

Timing of adverse effects: Up to 12 months

Factors that predict response: NR

Source citation: Baker et al. 2016[22]

Study Design: Nonrandomized comparative

Device Material: Mynx (AccessClosure, Inc.) vs. AngioSeal

Contact Duration: 30 days

Dose: NR

Frequency/ Duration: Single insertion of either 6 or 7 Fr sheath

Response: Access-site bleeding, Composite safety, Vascular injury

Patient characteristics (gender, mean age):

Number per group: Overall Population. Mynx: 65 years (SD 12), 34.5% female. AngioSeal: 64 years (SD 12), 35.0% female

Observed adverse effects: Overall Population (only percents reported)
Composite safety (access-site bleeding or hematoma, retroperitoneal bleeding, or any vascular complication requiring intervention)

Mynx: access-site bleeding (1.4%), composite safety (1.5%), vascular injury (0.8%)
AngioSeal: access-site bleeding (1.9%), composite safety (2.3%), vascular injury (0.3%)

Timing of adverse effects: Up to 30 days.

Factors that predict response: nr

ACS: acute coronary syndrome; NR: not reported; PEG: polyethylene glycol; RCT: randomized controlled trial; VCD: vascular closure device

Table 12: Mesh - Health Effect (In Vivo) Human Studies

Source citation: Lambrichts et al. 2018[26]

Study Design: Systematic review

Device Material: Parietex Composite (Medtronic)

Contact Duration: 12 months

Dose: NR

Frequency/ Duration: Single administration

Response: None reported

Patient characteristics (gender, mean age): NR.

Number per group: Of 4 included studies, only 1 case series (n=10) used PEG

Observed adverse effects: "No serious mesh-related or other serious complications were observed during 12 month follow-up."

Timing of adverse effects: N/A.

Factors that predict response: N/A.

Source citation: Thölix et al. 2018[28]

Study Design: Nonrandomized comparative

Device Material: Adhesix ([PEG] Cousin Biotech) vs. Parietex ProGrip ([non-PEG] Medtronic)

Contact Duration: Mean 18 months (Adhesix), 19 months (ProGrip)

Dose: Adhesix: 7.5 x 15.5 cm. ProGrip: 12 x 8 cm.

Frequency/ Duration: Single administration

Response: Hematoma, Pain, Seroma

Patient characteristics (gender, mean age): 97.5% male overall. Mean age 55 years (Adhesix), 53 years (ProGrip).

Number per group: 169 (Adhesix), 224 (ProGrip).

Observed adverse effects:
Hematoma: 1.2% (Adhesix), 1.8% (ProGrip).
Patients contacting providers due to pain: 2.4% (Adhesix), 8.5% (ProGrip); p = 0.01.
No hernia recurrence during follow-up in either group.
Seroma: 0.6% (Adhesix), 0.9% (ProGrip).

Timing of adverse effects: NR

Factors that predict response: NR

Source citation: Lambrecht et al. 2015[29]

Study Design: Single arm

Device Material: All patients received Parietex Composite (Medtronic)

Contact Duration: Mean 38 months

Dose: NR

Frequency/ Duration: Single administration

Response: Pain, Protrusion of mesh, Recurrence of hernia, Reoperations for bleeding and perforation, Seroma

Patient characteristics (gender, mean age): 62% female. Mean age 57 years.

Number per group: 107 overall.

Observed adverse effects:
Pain at 2 months: 27.1%
Protrusion of mesh: 10.3%
Recurrence: 2.8%
Reoperations for bleeding and perforation: 1.9%
Seroma: approximately 12%

Timing of adverse effects: NR

Factors that predict response: NR

Source citation: Canis et al. 2014[27]

Study Design: RCT

Device Material: PrevAdh ([PEG] Covidien) or Ringer's lactate solution

Contact Duration: 3 years

Dose: NR

Frequency/ Duration: Single administration

Response: None reported

Patient characteristics (gender, mean age): 100% female. Median age 34 years.

Number per group: 33 (PrevAdh), 28 (Ringer's).

Observed adverse effects: No device-related complications occurred in either group.

Timing of adverse effects: N/A

Factors that predict response: N/A

N/A: not applicable; PEG: PEG: polyethylene glycol; RCT: randomized controlled trial

Table 13: Embolic agent - Health Effect (In Vivo) Human Studies

Local Response/ Toxicity

Source citation: de Baere et al. 2020[30]

Study Design: Single arm

Device Material: LifePearl™ microspheres (Terumo Europe)

Contact Duration: Mean 7.2±6.5 months to last imaging; up to 20 months

Dose: 25.7% 100 µm, 74.3% 200 µm LifePearl; 25-150 mg doxorubicin, 5-20 mg idarubicin

Frequency/ Duration: Single DEM-TACE 45.4%,≥2 DEM-TACE 54.6%; total 187 DEM-TACE

Response: Chronic artery occlusion and stenosis of coronary ostium artery, False aneurysm of segment V in the liver, Hepatobiliary toxicities

Patient characteristics (gender, mean age): 92.8% male, 65.9±10.6 years.

Number per group: 97 patients with hepatocellular carcinoma (HCC) undergoing DEM-TACE (used as a bridge to liver transplant or downstaging to resection). LifePearl microspheres were loaded with anthracyclines (doxorubicin (77%) or idarubicin (23%)). Mean number of tumors per patient was 2.3±1.6

Observed adverse effects: Responses included chronic artery occlusion and stenosis of coronary ostium artery, and false aneurysm of segment V in the liver in 1 patient each.

Hepatobiliary toxicities (HBT)s were reported in 29 (30%) patients undergoing mean 2.4±1.4 DEM-TACE. 2 patients reported complications while HBTs were diagnosed by CT/MRI imaging in 27 patients. Rates of HBTs were not significantly different when LifePearl was loaded with idarubicin (10/31, 9.7%) or doxorubicin (26/156, 16.7%; p=0.58).

366 MRI/CT scans identified 9 bilomas (abnormal collection of bile outside the gallbladder; 2 detected at baseline), 9 portal vein thromboses (PVT) (5 detected at baseline), 2 portal vein branch narrowing (PVBN) (both detected at baseline), and 9 bile duct dilations (BDD) (1 detected at baseline). 10/29 (34%) patients experiencing HBTs had 1 to 7 prior liver-directed therapies (4 surgical resections, 6 thermal ablations, five cTACE, 2 each DEM-TACE and radioembolization).

Timing of adverse effects: Imaging was undertaken up to 20 months post DEM-TACE. HBTs identified at baseline were 2 bilomas, 5 PVTs, 2 PVBN, and 1 BDD. HBTs identified at first followup imaging (timing NR) was 1 PVT, 1 PVBN, and 1 biloma; all resolved.

Factors that predict response: NR.

Source citation: Gjoreski et al. 2019[31]

Study Design: Single arm

Device Material: LifePearl™ microspheres (Terumo Europe)

Contact Duration: Up to 12 months

Dose: 100 µm, 200 µm LifePearl, 75-150 mg of doxorubicin

Frequency/ Duration: ≥2 DEB-TACE (95%), 1 DEB-TACE (5%); total 54 DEM-TACE

Response: None reported

Patient characteristics (gender, mean age): 75% male, range 55 to 80 years

Number per group: 20 patients (29 tumors) with locally unresectable HCC. LifePearl microspheres were loaded with doxorubicin

Observed adverse effects: None observed

Timing of adverse effects: N/A

Factors that predict response: N/A

Systemic Response/ Toxicity

Source citation: de Baere et al. 2020[30]

Study Design: Single arm

Device Material: LifePearl™ microspheres (Terumo Europe)

Contact Duration: Mean 7.2±6.5 months to last imaging; up to 20 months, Dose: 25.7% 100 µm, 74.3% 200 µm

Frequency/ Duration: Single DEM-TACE 45.4%,≥2 DEM-TACE 54.6%; total 187 DEM-TACE

Response: Diarrhea, Facial cutaneous lesion, Fatigue, Hypertension Increase in ALT, AST, and bilirubin , Postembolization syndrome (PES) including abdominal pain.

Patient characteristics (gender, mean age): 92.8% male, 65.9±10.6 years

Number per group: 97 patients with HCC undergoing DEM-TACE. LifePearl microspheres were loaded with anthracyclines (doxorubicin (77%) or idarubicin (23%)).

Observed adverse effects: Most frequent AEs were PES. Grade 1-2 AEs in 71% patients. 21 SAEs (Grade ≥ 3) reported in 13 (13.4%) patients "related to LifePearl" included abdominal pain (6 patients),

diarrhea (2 cases in 1 patient); general health alteration (1 patient), and a facial cutaneous lesion (1 patient). Fatigue and hypertension occurred in 3 patients each while mild transient increase in ALT (10.3%), AST (7.2%), and bilirubin (6.2%) were also reported.

Timing of adverse effects: NR

Factors that predict response: NR

Source citation: Gjoreski et al. 2019[31]

Study Design: Single arm

Device Material: LifePearl™ microspheres (Terumo Europe)

Contact Duration: Up to 12 months

Dose: 100 µm, 200 µm LifePearl, 75-150 mg of doxorubicin

Frequency/ Duration: ≥2 DEB-TACE (95%), 1 DEB-TACE (5%); total 54 DEM-TACE

Response: PES including abdominal pain, fever, and nausea/vomiting

Patient characteristics (gender, mean age): 75% male, range 55 to 80 years.

Number per group: 20 patients (29 tumors) with locally unresectable HCC. LifePearl microspheres were loaded with doxorubicin

Observed adverse effects:

Occurrence of PES (Grade 1 or 2) following DEB-TACE

PES after 1st DEB-TACE (11/20, 55%), 2nd DEB-TACE (8/19, 42.1%), 3rd DEB-TACE (7/10, 70%), 4th DEB-TACE (2/3, 66.6%), 5th DEB-TACE (1/2, 50%)
Abdominal pain after 1st DEB-TACE (7/20, 35%), 2nd DEB-TACE (4/19, 21%), 3rd DEB-TACE (6/10, 60%), 4th DEB-TACE (1/3, 33.3%), 5th DEB-TACE (0/2, 0%)
Nausea/vomiting after 1st DEB-TACE (1/20, 5%), 2nd DEB-TACE (2/19, 10.5%), 3rd DEB-TACE (1/10, 10%), 4th DEB-TACE (1/3, 33.3%), 5th DEB-TACE (0/2, 0%)
Fever after 1st DEB-TACE (1/20, 5%), 2nd DEB-TACE (2/19, 10.5%), 3rd DEB-TACE (3/10, 30%), 4th DEB-TACE (0/3, 0%), 5th DEB-TACE (1/2, 50%)

Prolonged PES reported in 6 patients was followed by moderate abdominal pain, slightly elevated temperature, nausea/vomiting, and loss of appetite. Symptoms were resolved by day 4.

Acute pancreatitis occurred in 1 (5%) patient and was categorized as a procedure-related SAE since investigation showed reflux of drug-loaded microparticles in the superior panreatoduodenal artery

Timing of adverse effects: < day 4.

Factors that predict response: N/A.

AE: adverse event; ALT: alanine aminotransferase; AST: aspartate aminotransferase; CT: computer tomography; cTACE: conventional TACE; DEB-TACE: drug-eluting bead transarterial chemoembolization; DEM-TACE: transarterial chemoembolization with drug-eluting microspheres; MRI: magnetic resonance imaging; N/A: not applicable; NR: not reported; SAE: serious adverse event; TACE: transarterial chemoembolization; µm: microns

Table 14: Wound dressing - Health Effect (In Vivo) Human Studies

Local Response/ Toxicity

Source citation: Diaz-Molina et al. 2020[32]

Study Design: Nonrandomized comparative

Device Material: Hemopatch ([PEG] Baxter) vs. Tisseel ([non-PEG] Baxter)

Contact Duration: At least 6 months

Dose: NR

Frequency/ Duration: Single administration

Response: CSF leak, Epidural hematoma, Pseudomeningocele.

Patient characteristics (gender, mean age): 60.5% female, 56.8 years.

Number per group: Hemopatch (n = 82); Tisseel (n = 65).

Observed adverse effects: CSF leak rate was 3.6% (3/82) for Hemopatch, 13.8% (9/65) for Tisseel ($p < 0.05$ in bivariate analysis and multivariate model).
Epidural hematoma rate was 18.3% (15/82) for Hemopatch, 18.5% (12/65) for Tisseel ($p = 0.98$ in bivariate analysis).
Pseudomeningocele rate was 9.75% (8/82) for Hemopatch, 21.5% (14/65) for Tisseel ($p = 0.06$ in bivariate analysis, $p = 0.14$ in multivariate model).

Timing of adverse effects: NR (last follow-up occurred "at least 6 months after surgery").

Factors that predict response: NR (multivariate analysis was performed only on the combined sample).

Source citation: Ruggiero et al. 2016[33]

Study Design: Nonrandomized comparative

Device Material: Hemopatch ([PEG] Baxter) vs. standard hemostasis

Contact Duration: 3 months

Dose: NR

Frequency/ Duration: Single administration

Response: Drain output, Seroma

Patient characteristics (gender, mean age): 70% female, 42.3 years

Number per group: Hemopatch (n = 30); standard hemostasis (n = 30).

Observed adverse effects: Mean 24-hour drain output: Hemopatch, 50.1 ± 21.4 mL; standard hemostasis, 90.3 ± 24.2 mL ($p < 0.0001$). "Incidence of post-operative seroma was higher in standard hemostasis group." (No actual rates are given.)
No surgical or postsurgical complications reported in Hemopatch group. In standard hemostasis group, 3 patients had surgical complications and 2 developed temporary laryngeal nerve paralysis.

Timing of adverse effects: 24 hours (drain output); 3 months (complications)

Factors that predict response: NR.

CSF: cerebrospinal fluid; NR: not reported; PEG: polyethylene glycol

Table 15: Bone filler/grafting - Health Effect (In Vivo) Human Studies

Source citation: Jung et al. 2020[34]

Study Design: RCT

Device Material: MembraGel ([PEG] Straumann) vs. BioGide ([collagen] Geistlich)

Contact Duration: 18 months

Dose: NR

Frequency/ Duration: Single application

Response: Dehiscences

Patient characteristics (gender, mean age): 68.2% female, mean age 48.7 years

Number per group: 60 per group; 57 in each group provided 6-month data.

Observed adverse effects:

The number of patients in the PEG group with dehiscences were 4 at 7-10 days, 4 at 12-14 days, 3 at 4 weeks, 3 at 3 months, 2 at 6 months, and 1 at 18 months. For BioGide, the numbers were 8, 8, 7, 6, 4, and 0. Differences between the groups were not statistically significant.

30 adverse events were noted overall, including infection, inflammation, swelling, allergy, pain, cancer, and cerebral infarction, among others. 30% of all PEG patients had adverse events, compared to 10.5% of all BioGide patients.

Timing of adverse effects: 24 of 30 adverse events occurred during the first 6 months

Factors that predict response: NR.

Source citation: Ramel et al. 2012[35]

Study Design: RCT

Device Material: MembraGel ([PEG] Straumann) vs. BioGide ([collagen] Geistlich)

Contact Duration: 3 years

Dose: NR

Frequency/ Duration: Single administration

Response: No dehiscences, Periodontal status

Patient characteristics (gender, mean age): NR.

Number per group: 18.

Observed adverse effects: No dehiscences in either group; periodontal status was normal in all patients

Timing of adverse effects: N/A.

Factors that predict response: N/A.

PEG: polyethylene glycol; RCT: randomized controlled trial

Table 16: Hydrogel spacer - Health Effect (In Vivo) Human Studies

Local Response/ Toxicity.

Source citation: Dinh et al. 2020[40]

Study Design: Nonrandomized comparative

Device Material: SpaceOAR (Augmenix) vs. Rectal balloon

Contact Duration: 2 years

Dose: SpaceOAR: NR Rectal balloon: 90 mL water

Frequency/ Duration: SpaceOAR: single administration, Rectal balloon: multiple administration

Response: G1+ Complications + Bleeding, G2+ Complications + Bleeding, G3+ Complications + Bleeding

Patient characteristics (gender, mean age):
SpaceOAR: 68.7 years (SD 6.3), 0% female
Rectal Balloon: 67.9 years (SD 6.9), 0% female

Number per group: SpaceOAR: 75; Rectal Balloon: 192

Observed adverse effects:
SpaceOAR: G1+ bleeding (actuarial rate of 13%), G2+ bleeding (actuarial rate of 3%), no events of G3+ or G4+ bleeding.
Rectal balloon: G1+ bleeding (actuarial rate of 35%), G2+ bleeding (actuarial rate of 19%), 3 events of G3+ bleeding, no events of G4+ bleeding.
G1+ bleeding: HR 0.287 (95% CI 0.137 to 0.601), p<0.001, favors spacer
G2+ bleeding: HR 0.145 (95% CI 0.034 to 0.641), p=0.010, favors spacer

Timing of adverse effects: Up to 2 years.

Factors that predict response: NR

Source citation: Vaggers et al. 2020[4]

Study Design: Systematic review

Device Material: SpaceOAR ([PEG] Boston Scientific, Augmenix), vs. DuraSeal ([PEG] Integra LifeSciences)

Contact Duration: Median follow up: range 6 to 60 months

Dose: NR

Frequency/ Duration: NR

Response: Diarrhea, Fistula, G1 Complications, G2 Complications, Proctitis

Patient characteristics (gender, mean age): NR.

Number per group: DuraSeal: 3 single arm studies: 347 total patients; 1 nonrandomized comparative study: 100 patients with DuraSeal vs. 100 patients without DuraSeal

SpaceOAR: 5 nonrandomized comparative studies: 254 with SpaceOAR, 502 without SpacceOAR.

Observed adverse effects: SpaceOAR: Two studies reporting on late GI toxicity found no difference (p<0.05) in late G1 GI complications. Acute GI toxicity events varied by study. 2 studies reported significant differences in acute G1 complications favoring gel over no gel; no difference in acute G2 complications. One study divided patients by treatment technique and found mixed results on diarrhea and minimal instances of proctitis within one study arm (salvage LDR-BT). No study found any G3 or 4 acute complications. DuraSeal: see Table 2 for results.

Timing of adverse effects: Up to 6 or 60 months

Factors that predict response: NR

Source citation: Aminsharifi et al. 2019[37]

Study Design: Systematic review

Device Material: SpaceOAR (Augmenix)

Contact Duration: 15 months to 3 years

Dose: NR

Frequency/ Duration: Single administration

Response:
Perineal abscess requiring drainage
Perineal abscess—subsequent death
Perirectal fistula requiring surgical intervention
Proctitis requiring colostomy
Prostatic abscess requiring drainage
Purulent drainage from perineum requiring antibiotics
Rectal ulcer and hemorrhage requiring surgery
Rectal wall erosion—no sequelae
Rectourethral fistula requiring colostomy
Tenesmus with air in rectal wall—no sequelae
Venous injection—no sequelae

Patient characteristics (gender, mean age): NR.

Number per group: 25 total AEs (n=22) voluntarily reported in the MAUDE database (January 2015 to March 2019) and related to injection of SpaceOAR before radiotherapy for prostate cancer. The manufacturer's website was also reviewed for device-related complications

Observed adverse effects:
4 rectourethral fistula requiring colostomy (Level III harm), 3 perineal abscess requiring drainage (Level III harm), 3 venous injection—no sequelae (Level I harm),1 perirectal fistula requiring surgical intervention (Level III harm), 1 proctitis requiring colostomy (Level III harm), 1 purulent drainage from perineum requiring antibiotics (Level II harm), 1 rectal ulcer and hemorrhage requiring surgery (Level III), 1 rectal wall erosion—no sequelae (Level I harm), 1 tenesmus with air in rectal wall—no sequelae (Level I harm), 1 prostatic abscess requiring drainage (Level III harm)

Timing of adverse effects: NR

Factors that predict response: NR

Source citation: te Velde et al. 2019[39]

Study Design: Nonrandomized comparative

Device Material: SpaceOAR (Aumenix) vs. non-SpaceOAR

Contact Duration: Between 3 months and 3 years

Dose: Rectal doses: V40 Gy < 35%,

V65 Gy < 17%,

V75 Gy < 10%.

Frequency/ Duration: Single administration

Response: Diarrhea (G1 and G2), Fecal incontinence (G1 and G2), Hemorrhoids (G1 and G2), Proctitis (G1 and G2)

Patient characteristics (gender, mean age):
SpaceOAR: Median 71.5 years (Range 56.9 to 86.6 years), 0% female;
Non-SpaceOAR: Median 72.3 years (Range 54.2 to 86.0 years), 0% female

Number per group: SpaceOAR: 65; Non-SpaceOAR: 56.

Observed adverse effects:

Cumulative Incidence
Diarrhea (G1): SpaceOAR: 6.2%, Non-SpaceOAR: 21.4%; Diarrhea (G2): SpaceOAR: 1.5%, Non-SpaceOAR: 0%;
Fecal incontinence (G1): SpaceOAR: 1.5%, Non-SpaceOAR: 3.6%; Fecal incontinence (G2): SpaceOAR: 0%, Non-SpaceOAR: 0%;
Proctitis (G1): SpaceOAR: 9.2%, Non-SpaceOAR: 19.6%; Proctictis (G2): SpaceOAR: 0%, Non-SpaceOAR: 7.1%;
Hemorrhoids (G1): SpaceOAR: 16.9%, Non-SpaceOAR: 12.5%; Hemorrhoids (G2): SpaceOAR: 1.5%, Non-SpaceOAR: 1.8%

Baseline Corrected
Diarrhea (G1): SpaceOAR: 1.7%, Non-SpaceOAR: 7.3%; Diarrhea (G2): SpaceOAR: 0%, Non-SpaceOAR: 0%;
Fecal incontinence (G1): SpaceOAR: 0%, Non-SpaceOAR: 0%; Fecal incontinence (G2): SpaceOAR: 0%, Non-SpaceOAR: 0%;
Proctitis (G1): SpaceOAR: 1.7%, Non-SpaceOAR: 3.6%; Proctictis (G2): SpaceOAR: 0%, Non-SpaceOAR: 3.6%;
Hemorrhoids (G1): SpaceOAR: 5.0%, Non-SpaceOAR: 7.3%; Hemorrhoids (G2): SpaceOAR: 1.7%, Non-SpaceOAR: 1.8%

Timing of adverse effects:
3 years after Radiation Therapy
Diarrhea (G1): SpaceOAR: 1.7%, Non-SpaceOAR: 5.5%; Diarrhea (G2): SpaceOAR: 0%, Non-SpaceOAR: 0%;
Fecal incontinence (G1): SpaceOAR: 0%, Non-SpaceOAR: 0%; Fecal incontinence (G2): SpaceOAR: 0%, Non-SpaceOAR: 0%;
Proctitis (G1): SpaceOAR: 1.7%, Non-SpaceOAR: 5.5%; Proctictis (G2): SpaceOAR: 0%, Non-SpaceOAR: 1.8%;
Hemorrhoids (G1): SpaceOAR: 15.0%, Non-SpaceOAR: 9.1%; Hemorrhoids (G2): SpaceOAR: 1.7%, Non-SpaceOAR: 1.8%

Factors that predict response: NR

Source citation: te Velde et al. 2017[38]

Study Design: Nonrandomized comparative

Device Material: SpaceOAR (Aumenix) vs. non-SpaceOAR

Contact Duration: Up to 12 weeks

Dose: Rectal Doses: V40 Gy < 35%, V65 Gy < 17%, V75 Gy < 10%.

Frequency/ Duration: Single administration

Response: Diarrhea (G1 and G2), Fecal incontinence (G1 and G2), Hemorrhoids (G1 and G2), Proctitis (G1 and G2)

Patient characteristics (gender, mean age): SpaceOAR: Median 71.5 years, 0% female; Non-SpaceOAR: Median 72.3 years, 0% female

Number per group: SpaceOAR: 65; Non-SpaceOAR: 60.

Observed adverse effects:
During Radiation Therapy:
Diarrhea (G1): SpaceOAR: 13.8%, Non-SpaceOAR: 31.7%; Diarrhea (G2): SpaceOAR: 0%, Non-SpaceOAR: 0%;
Fecal incontinence (G1): SpaceOAR: 3.1%, Non-SpaceOAR: 3.3%; Fecal incontinence (G2): SpaceOAR: 0%, Non-SpaceOAR: 0%
Proctitis (G1): SpaceOAR: 9.2%, Non-SpaceOAR: 13.3%; Proctictis (G2): SpaceOAR: 4.6%, Non-SpaceOAR: 1.7%

Hemorrhoids (G1): SpaceOAR: 23.1%, Non-SpaceOAR: 20.0%; Hemorrhoids (G2): SpaceOAR: 4.6%, Non-SpaceOAR: 3.3%

Timing of adverse effects: 12 weeks after Radiation Therapy
Diarrhea (G1): SpaceOAR: 4.6%, Non-SpaceOAR: 5.0%; Diarrhea (G2): SpaceOAR: 0%, Non-SpaceOAR: 0%;
Fecal incontinence (G1): SpaceOAR: 0%, Non-SpaceOAR: 1.7; Fecal incontinence (G2): SpaceOAR: 0%, Non-SpaceOAR: 0%;
Proctitis (G1): SpaceOAR: 1.5%, Non-SpaceOAR: 5.0%; Proctictis (G2): SpaceOAR: 0%, Non-SpaceOAR: 0%;
Hemorrhoids (G1): SpaceOAR: 3.1%, Non-SpaceOAR: 11.7%; Hemorrhoids (G2): SpaceOAR: 0%, Non-SpaceOAR: 0%.

Factors that predict response: NR

Source citation: Mok et al. 2014[36]

Study Design: Systematic review

Device Material: SpaceOAR (Aumenix);
non-PEG devices (collagen implants, hyaluronic acid spacers)

Contact Duration: 12 months

Dose: NR

Frequency/ Duration: NR

Response: Acute GI Toxicity (G1 and G2), Acute GU toxicity (G1, G2, and G3), Diarrhea (G1, G2, or G3), Focal rectal mucosal necrosis and bladder perforation, Late GI Toxicity (G1), Late GU toxicity (G1 and G2), Telangiectasia (G1, G2, and G3), Urinary obstruction (G1)

Patient characteristics (gender, mean age): NR. Patients with localized prostate cancer treated by curative radiation therapy

Number per group: SpaceOAR (n=5 studies); collagen (n=1 study); hyaluronic acid (n=5 studies)

Observed adverse effects:
SpaceOAR
One study reported 3 patients with focal rectal mucosal necrosis and bladder perforation (prior to routine use of transrectal ultrasonography (TRUS) guidance). Remaining studies reported 39.6% acute G1 GI toxicity, 12.5% acute G2 GI toxicity, 4.3% late G1 GI toxicity, 41.7% acute G1 GU toxicity, 35.4% acute G2 GU toxicity, 2.1% acute G3 GU toxicity, 17% late G1 GU toxicity, 2.1% late G2 GU toxicity, 13% G1 telangiectasia, 13% G2 telangiectasia, and 2% G3 telangiectasia.

Non-PEG Devices
6 studies reviewing non-PEG devices found various incidence rates regarding complications. One collagen study found five out of 11 patients experiencing urinary obstructions, although, no acute or late GI toxicities were reported. One study found a low incidence (5%) of rectal mucosal damage for hyaluronic acid implants. One study reported 12.5% incidence of anal mucositis (acute grade 1 GI), 2.5% urinary obstruction (mild grade 1), 27.5% with urinary obstruction, and 29.7% with diarrhea (grade 1 GI).

Timing of adverse effects:
SpaceOAR
Up to 12 months (only one study reports f/u)
Non-PEG Devices
Up to 19 months (only one study reports f/u).

Factors that predict response: NR

Systemic Response/ Toxicity.

Source citation: Aminsharifi et al. 2019[37]

Study Design: Systematic review

Device Material: SpaceOAR (Augmenix)

Contact Duration: 15 months to 3 years

Dose: NR

Frequency/ Duration: Single administration

Response: Diagnosed pulmonary embolism requiring anticoagulant, Dizziness/nausea postprocedure leading to unresponsiveness and death, Perineal abscess—subsequent death , Severe anaphylactic reaction, Severe urosepsis—ICU care

Patient characteristics (gender, mean age): NR

Number per group: 25 total AEs (n=22) reported in the MAUDE database (January 2015 to March 2019) and related to injection of SpaceOAR before radiotherapy for prostate cancer. The manufacturer's website was also reviewed for device-related complications

Observed adverse effects:

Level 2 harms
4 diagnosed pulmonary embolism requiring anticoagulant

Level IV harms
1 dizziness/nausea postprocedure leading to unresponsiveness and death (unclear if device-related), 1 perineal abscess—subsequent death from alcoholic cardiomyopathy (unclear if device-related), 1 severe anaphylactic reaction, 1 severe urosepsis—ICU care

Timing of adverse effects: NR

Factors that predict response: NR

f/u: follow up; G1: Grade 1; G2: Grade 2; G3: Grade 3; G4: Grade 4; GI: gastrointestinal; GU: genitourinary; MAUDE: Manufacturer and User Facility Device Experience; V40 Gy: 40 gray; V65 Gy: 65 gray; V75 Gy: 75 gray

Table 17: Eye surgery dye - Health Effect (In Vivo) Human Studies

Local Response/ Toxicity

Source citation:

Study Design:

Device Material:

Contact Duration:

Dose:

Frequency/ Duration:

Response:

Patient characteristics (gender, mean age):

Number per group:

Observed adverse effects:

Timing of adverse effects:

Factors that predict response:

Table 18: Eye surgery dye - Health Effect (In Vivo) Human Studies

Source citation: Veckeneer et al. 2014[41]

Study Design: Nonrandomized comparative

Device Material: ILM-Blue™ and MembraneBlue-Dual™; both 4% PEG (D.O.R.C. International)

Contact Duration: Up to 12 months

Dose: 0.1 ml applied onto the macula

Frequency/ Duration: Second dye application:

25/63 (40%) MembraneBlue-Dual, 21/64 (33%) ILM-Blue

Response: None reported

Patient characteristics (gender, mean age): 55% male, mean 68±1.3 years

Number per group: 127 patients (127 eyes) undergoing macular surgery: 64 ILM-Blue, 63 MembraneBlue-Dual

Observed adverse effects: No complications or side effects were observed up to 12 months

Timing of adverse effects: N/A.

Factors that predict response: N/A.

Appendix E. References

1. Thoma DS, Dard MM, Hälg GA, Ramel CF, Hämmerle CH, Jung RE. Evaluation of a biodegradable synthetic hydrogel used as a guided bone regeneration membrane: an experimental study in dogs. Clin Oral Implants Res. 2012 Feb;23(2):160-8. Also available: http://dx.doi.org/10.1111/j.1600-0501.2011.02217.x. PMID: 21692857.

2. Rashid HQ, Karabulut E, Cevik A. Effectiveness of polypropylene mesh coated bovine amniotic membrane with adhesion barrier (polyethylene glycol) in repair of abdominal wall hernias in rats. Indian J Anim Sci. 2018 Sep;88(9):1010-4. Also available: https://www.researchgate.net/publication/328267301_Effectiveness_of_polypropylene_mesh_coated_bovine_amniotic_membrane_with_adhesion_barrier_polyethylene_glycol_in_repair_of_abdominal_wall_hernias_in_rats.

3. Tan J, Foster LJ, Watson SL. Corneal sealants in clinical use: a systematic review. Curr Eye Res. 2020 Sep;45(9):1025-30. Also available: http://dx.doi.org/10.1080/02713683.2020.1764052. PMID: 32460646.

4. Vaggers S, Rai BP, Chedgy EC, de la Taille A, Somani BK. Polyethylene glycol-based hydrogel rectal spacers for prostate brachytherapy: a systematic review with a focus on technique. World J Urol. 2020 Aug 25;Online ahead of print. Also available: http://dx.doi.org/10.1007/s00345-020-03414-6. PMID: 32840655.

5. Khoynezhad A, DelaRosa J, Moon MR, Brinkman WT, Thompson RB, Desai ND, Malaisrie SC, Girardi LN, Bavaria JE, Reece TB. Facilitating hemostasis after proximal aortic surgery: results of the PROTECT trial. Ann Thorac Surg. 2018 May;105(5):1357-64. Also available: http://dx.doi.org/10.1016/j.athoracsur.2017.12.013. PMID: 29337125.

6. Wright NM, Park J, Tew JM, Kim KD, Shaffrey ME, Cheng J, Choudhri H, Krishnaney AA, Graham RS, Mendel E, Simmons N. Spinal sealant system provides better intraoperative watertight closure than standard of care during spinal surgery: a prospective, multicenter, randomized controlled study. Spine (Phila Pa 1976). 2015 Apr 15;40(8):505-13. Also available: http://dx.doi.org/10.1097/BRS.0000000000000810. PMID: 25646746.

7. De Leyn P, Muller MR, Oosterhuis JWA, Schmid T, Choong CKC, Weder W, Sokolow Y. Prospective European multicenter randomized trial of PleuraSeal for control of air leaks after elective pulmonary resection. J Thorac Cardiovasc Surg. 2011 Apr;141(4):881-7. Also available: http://dx.doi.org/10.1016/j.jtcvs.2010.09.019. PMID: 21093877.

8. Trew GH, Pistofidis GA, Brucker SY, Krämer B, Ziegler NM, Korell M, Ritter H, McConnachie A, Ford I, Crowe AM, Estridge TD, Diamond MP, De Wilde RL. A first-in-human, randomized, controlled, subject- and reviewer-blinded multicenter study of Actamax™ Adhesion Barrier. Arch Gynecol Obstet. 2017 Feb 1;295(2):383-95. Also available: http://dx.doi.org/10.1007/s00404-016-4211-x. PMID: 27844212.

9. Tew JM, Strong MJ, Alexanderwest G, Woo H, Couture DE, Wilson JA, Munoz LF, Rosen CL, Greenlee JD, Van Loveren HR, Iantosca M, Baird CJ, Smith M, McGirt M, Parish J, Asher AL. A pivotal randomized clinical trial evaluating the safety and effectiveness of a novel hydrogel dural sealant as an adjunct to dural repair. Oper Neurosurg (Hagerstown). 2017;13(2):204-12. Also available: http://dx.doi.org/10.1093/ons/opw004. PMID: 28927211.

10. Gologorsky RC, Alabaster AL, Ashiku SK, Patel AR, Velotta JB. Progel use is not associated with decreased incidence of postoperative air leak after nonanatomic lung surgery. Perm J. 2019;23:18-059. Also available: http://dx.doi.org/10.7812/TPP/18-059. PMID: 30939277.

11. Zhou X, Goodwin CR, Recinos PF, Yang JX, Jallo GI. Evaluation of complication rates of pediatric cranial procedures in which a polyethylene glycol sealant was used. J Neurosurg Pediatr. 2014 Nov 1;14(5):514-7. Also available: http://dx.doi.org/10.3171/2014.7.PEDS1437. PMID: 25192234.

12. Lareyre F, Mialhe C, Dommerc C, Mbeutcha A, Raffort J. Endovascular aneurysm sealing as an alternative for the treatment of failed endovascular aneurysm repair. Vascular. 2020 Jun;28(3):251-8. Also available: http://dx.doi.org/10.1177/1708538119897525. PMID: 31896300.

13. Choo XY, Hajibandeh S, Hajibandeh S, Antoniou GA. The Nellix endovascular aneurysm sealing system: current perspectives. Med Devices Evid Res. 2019;12:65-79. Also available: http://dx.doi.org/10.2147/MDER.S155300.

14. Martinelli O, Di Girolamo A, Irace L, Baratta F, Gossetti B, Gattuso R. Post-implantation syndrome: the impact of different devices for endovascular abdominal aortic aneurysm repair and related etiopathogenetic implications. Int Angiol. 2020 Oct;39(5):398-404. Also available: http://dx.doi.org/10.23736/S0392-9590.20.04163-2. PMID: 32401471.

15. Ten Broek RP, Stommel MW, Strik C, Van Laarhoven CJ, Keus F, Van Goor H. Benefits and harms of adhesion barriers for abdominal surgery: a systematic review and meta-analysis. Lancet. 2014;383(9911):48-59. Also available: http://dx.doi.org/10.1016/S0140-6736(13)61687-6. PMID: 24075279.

16. Banasiewicz T, Horbacka K, Karo J, Malinger S, Antos F, Rudzki S, Kala Z, Stojcev Z, Kössi J, Krokowicz P. Preliminary study with SprayShield™ adhesion barrier system in the prevention of abdominal adhesions. Wideochir I Inne Tech Maloinwazyjne. 2013;8(4):301-9. Also available: http://dx.doi.org/10.5114/wiitm.2011.34884.

17. Rhyne AL, Blumenthal SL, Frank EH, Hsu KY, Kim KD, Youssef JA, Wang JC, Arnold P, Bendebba M, Block KM, Juarez TG, Chiacchierini RP, Ehmsen RJ, Krelle JS, Dizerega GS. Oxiplex reduces leg pain, back pain, and associated symptoms after lumbar discectomy. Spine (Phila Pa 1976). 2012 Apr 15;37(8):631-41. Also available: http://dx.doi.org/10.1097/BRS.0b013e3182309af7. PMID: 21897344.

18. Di Spiezio Sardo A, Spinelli M, Bramante S, Scognamiglio M, Greco E, Guida M, Cela V, Nappi C. Efficacy of a polyethylene oxide-sodium carboxymethylcellulose gel in prevention of intrauterine adhesions after hysteroscopic surgery. J Minim Invasive Gynecol. 2011 Jul-Aug;18(4):462-9. Also available: http://dx.doi.org/10.1016/j.jmig.2011.04.007. PMID: 21777835.

19. Noori VJ, Eldrup-Jørgensen J. A systematic review of vascular closure devices for femoral artery puncture sites. J Vasc Surg. 2018 Sep;68(3):887-99. Also available: http://dx.doi.org/10.1016/j.jvs.2018.05.019. PMID: 30146036.

20. Kennedy SA, Rajan DK, Bassett P, Tan KT, Jaberi A, Mafeld S. Complication rates associated with antegrade use of vascular closure devices: a systematic review and pooled analysis. J Vasc Surg. 2021 Feb;73(2):722-730.e1. Also available: http://dx.doi.org/10.1016/j.jvs.2020.08.133. PMID: 32950629.

21. Ben-Dor I, Craig P, Torguson R, Rogers T, Buchanan KD, Pokharel S, Gai J, Okubagzi PG, Satler LF, Pichard AD, Baker NC, Waksman R. MynxGrip® vascular closure device versus manual compression for hemostasis of percutaneous transfemoral venous access closure: results from a prospective multicenter randomized study. Cardiovasc Revasc Med. 2018 Jun;19(4):418-22. Also available: http://dx.doi.org/10.1016/j.carrev.2018.03.007. PMID: 29656937.

22. Baker NC, Escarcega RO, Lipinski MJ, Magalhaes MA, Koifman E, Kiramijyan S, Negi SI, Torguson R, Waksman R. Active versus passive anchoring vascular closure devices following percutaneous coronary intervention: a safety and efficacy comparative analysis. J Interv Cardiol. 2016 Feb 1;29(1):108-12. Also available: http://dx.doi.org/10.1111/joic.12264. PMID: 26728544.

23. Jones LE, Yang KH, Feldtman RW, Uceda PV, Ferrara CA, Caruso JM, Richmond JL, Ahn SS. Safety and efficacy of arterial closure devices in an office-based angiosuite. Ann Vasc Surg. 2018 Aug;51:10-7. Also available: http://dx.doi.org/10.1016/j.avsg.2018.02.011. PMID: 29655814.

24. Resnic FS, Majithia A, Marinac-Dabic D, Robbins S, Semaganda H, Hewitt K, Ponirakis A, Loyo-Berrios N, Moussa I, Drozda J, Normand SL, Matheny ME. Registry-based prospective, active surveillance of medical-device safety. N Engl J Med. 2017 Feb 9;376(6):526-35. Also available: http://dx.doi.org/10.1056/NEJMoa1516333. PMID: 28121489.

25. Elmasri MA, Kee ST, Moriarty JM, Gomes A, Lee EW, McWilliams JP. Single-center comparison of the efficacy and complications of arterial vascular closure devices in interventional radiology. J Vasc Access. 2017;18(4):339-44. Also available: http://dx.doi.org/10.5301/jva.5000623. PMID: 28665467.

26. Lambrichts DP, de Smet GH, van der Bogt RD, Kroese LF, Menon AG, Jeekel J, Kleinrensink GJ, Lange JF. Incidence, risk factors and prevention of stoma site incisional hernias: a systematic review and meta-analysis. Colorectal Dis. 2018 Oct 1;20(10):O288-O303. Also available: http://dx.doi.org/10.1111/codi.14369. PMID: 30092621.

27. Canis MJ, Triopon G, Daraï E, Madelenat P, Levêque J, Panel P, Fernandez H, Audebert A, Descamps P, Castaing N, Roman H, Fauconnier A, Benifla JL. Adhesion prevention after myomectomy by laparotomy: a prospective multicenter comparative randomized single-blind study with second-look laparoscopy to assess the effectiveness of PREVADH™. Eur J Obstet Gynecol Reprod Biol. 2014 Jul;178:42-7. Also available: http://dx.doi.org/10.1016/j.ejogrb.2014.03.020. PMID: 24841647.

28. Thölix AM, Kössi J, Remes V, Scheinin T, Harju J. Lower incidence of postoperative pain after open inguinal hernia surgery with the usage of synthetic glue-coated mesh (Adhesix). Am Surg. 2018 Dec;84(12):1932-7. PMID: 30606351.

29. Lambrecht JR, Vaktskjold A, Trondsen E, Øyen OM, Reiertsen O. Laparoscopic ventral hernia repair: outcomes in primary versus incisional hernias: no effect of defect closure. Hernia. 2015 Feb 7;19(3):479-86. Also available: http://dx.doi.org/10.1007/s10029-015-1345-x. PMID: 25663605.

30. de Baere T, Guiu B, Ronot M, Chevallier P, Sergent G, Tancredi I, Tselikas L, Burgio MD, Raynaud L, Deschamps F, Verset G. Real life prospective evaluation of new drug-eluting platform for chemoembolization of patients with hepatocellular carcinoma: Paris registry. Cancers. 2020 Nov 1;12(11):1-15. Also available: http://dx.doi.org/10.3390/cancers12113405.

31. Gjoreski A, Popova-Jovanovska R, Eftimovska-Rogac I, Vejseli J. Safety profile and efficacy of chemoembolization with doxorubicin - loaded polyethylene glycol microspheres in patients with hepatocellular carcinoma. Open Access Maced J Med Sci. 2019 Mar 15;7(5):742-6. Also available: http://dx.doi.org/10.3889/oamjms.2019.179.

32. Diaz-Molina J, Martinez Ri, Gonzalez-Vargas P, Calero L, Azevedo A, Conde C. Tisseel® versus Hemopatch® for dural sealing in neurosurgery. A prospective study in a tertiary center. Neurochirurgie. 2020 Dec;66(6):429-34. Also available: http://dx.doi.org/10.1016/j.neuchi.2020.09.008. PMID: 33091461.

33. Ruggiero R, Docimo L, Tolone S, De Palma M, Musella M, Pezzolla A, Gubitosi A, Parmeggiani D, Pirozzi R, Gili S, Parisi S, D'Alessandro A, Docimo G. Effectiveness of an advanced hemostatic pad combined with harmonic scalpel in thyroid surgery. A prospective study. Int J Surg. 2016 Apr;28 Suppl 1:S17-21. Also available: http://dx.doi.org/10.1016/j.ijsu.2015.12.044. PMID: 26708861.

34. Jung RE, Mihatovic I, Cordaro L, Windisch P, Friedmann A, Blanco Carrion J, Sanz Sanchez I, Hallman M, Quirynen M, Hammerle CH. Comparison of a polyethylene glycol membrane and a collagen membrane for the treatment of bone dehiscence defects at bone level implants-a prospective, randomized, controlled, multicenter clinical trial. Clin Oral Implants Res. 2020 Nov;31(11):1105-15. Also available: http://dx.doi.org/10.1111/clr.13657. PMID: 32875638.

35. Ramel CF, Wismeijer DA, Hämmerle CH, Jung RE. A randomized, controlled clinical evaluation of a synthetic gel membrane for guided bone regeneration around dental implants: clinical and radiologic 1- and 3-year results. Int J Oral Maxillofac Implants. 2012 Mar-Apr;27(2):435-41. PMID: 22442785.

36. Mok G, Benz E, Vallee JP, Miralbell R, Zilli T. Optimization of radiation therapy techniques for prostate cancer with prostate-rectum spacers: a systematic review. Int J Radiat Oncol Biol Phys. 2014 Oct 1;90(2):278-88. Also available: http://dx.doi.org/10.1016/j.ijrobp.2014.06.044. PMID: 25304788.

37. Aminsharifi A, Kotamarti S, Silver D, Schulman A. Major complications and adverse events related to the injection of the SpaceOAR hydrogel system before radiotherapy for prostate cancer: review of the manufacturer and user facility device experience database. J Endourol. 2019 Oct 1;33(10):868-71. Also available: http://dx.doi.org/10.1089/end.2019.0431. PMID: 31452385.

38. te Velde BL, Westhuyzen J, Awad N, Wood M, Shakespeare TP. Can a peri-rectal hydrogel SpaceOAR programme for prostate cancer intensity-modulated radiotherapy be successfully implemented in a regional setting? J Med Imaging Radiat Oncol. 2017 Aug;61(4):528-33. Epub 2017 Feb 2. Also available: http://dx.doi.org/10.1111/1754-9485.12580. PMID: 28151584.

39. te Velde BL, Westhuyzen J, Awad N, Wood M, Shakespeare TP. Late toxicities of prostate cancer radiotherapy with and without hydrogel SpaceAOR insertion. J Med Imaging Radiat Oncol. 2019 Dec 1;63(6):836-41. Also available: http://dx.doi.org/10.1111/1754-9485.12945. PMID: 31520465.

40. Dinh TK, Lee HJ, Macomber MW, Apisarnthanarax S, Zeng J, Laramore GE, Rengan R, Russell KJ, Chen JJ, Ellis WJ, Schade GR, Liao JJ. Rectal hydrogel spacer improves late gastrointestinal toxicity compared to rectal balloon immobilization after proton beam radiation therapy for localized prostate cancer: a retrospective observational study. Int J Radiat Oncol Biol Phys. 2020 Nov;108(3):635-43. Also available: http://dx.doi.org/10.1016/j.ijrobp.2020.01.026. PMID: 32035187.

41. Veckeneer M, Mohr A, Alharthi E, Azad R, Bashshur ZF, Bertelli E, Bejjani RA, Bouassida B, Bourla D, Crespo IC, Fahed C, Fayyad F, Mura M, Nawrocki J, Rivett K, Scharioth GB, Shkvorchenko DO, Szurman P, Van Wijck H, Wong IY, Wong DS, Frank J, Oellerich S, Bruinsma M, Melles GR. Novel 'heavy' dyes for retinal membrane staining during macular surgery: multicenter clinical assessment. Acta Ophthalmol. 2014;92(4):339-44. Also available: http://dx.doi.org/10.1111/aos.12208. PMID: 23782673.

Appendix F. Surveillance Event Reports - PSO and Accident Investigation

Provided with this report as separate Excel spreadsheet.

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.