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Medical Device Material Performance Study

Polyurethane Safety Profile

Prepared for
U.S. FDA Center for Devices and Radiological Health

Submitted to

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Table of Contents

Table of Tables

Executive Summary

Key Points

1. Searches identified 2,546 citations; 82 articles were selected for inclusion.
2. The local responses/events reported in the largest number of studies were mild inflammation, catheter dysfunction, phlebitis, and thrombosis, and they were associated with moderate quality of evidence. Other local responses for PUR devices were associated with low or very low quality of evidence.
3. It is not clear in the literature whether reported device malfunctions were related to biocompatibility or device integrity.
4. No Studies that met inclusion criteria investigated systemic reactions to PUR devices.
5. The most common complication in ECRI surveillance data for PUR devices was related to device malfunction or failure.
6. Evidence gaps:
    a. Systemic response to all PUR as a material and all devices. There was no included literature that reported on systemic response.
    b. PUR device failure as a function of material response due to insufficient biocompatibility or device use.
    c. Patient or material related factors for local response to PUR devices.

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. 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 PUR. 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 PUR?**

    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. Intravascular catheters had the largest literature base (almost all were human studies). Local responses/device events included catheter dysfunction, phlebitis, and thrombosis. Blood access devices (human studies) and catheter securement devices (human studies) also reported catheter dysfunction and thrombosis.
        ii. Studies of PUR as a material (predominantly animal studies) reported mild local inflammatory responses (including foreign body reaction). Within this category, studies of blood vessel grafts frequently reported graft patency/occlusion.
        iii. Studies of cardiovascular pacemaker electrodes reported lead failure, lead dislodgement, and severe insulation damage.
        iv. The overall quality of evidence related to local host responses was moderate to very low, with variation across different device categories.
        v. Very little evidence was found regarding local host responses for ventricular assist devices and neurostimulation devices.
        vi. No evidence was found regarding local host responses for pacemaker repair or replacement material, implanted electrical urinary/fecal continence devices.

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

i. Studies evaluated inflammation following PUR material exposure during periods ranging from 1 week to 6 months, with most follow-up being 3 months or less.
ii. Studies of catheters or blood access devices evaluated catheter dysfunction, phlebitis and thrombosis over follow-up ranging from a few days to 3 years.
iii. Studies of cardiovascular pacemaker electrode recorded lead failure, lead dislodgement or severe insulation damage over periods ranging from 25 to 82 months.

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?

No studies reported data regarding systemic manifestations related to PUR devices. The quality of evidence is therefore very low.

b. What are the likely systemic manifestations?

No systemic manifestations were reported in the literature, which suggests that such manifestations are either very rare or not a problem with PUR devices.

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

See above.

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

See above.

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?

Since no studies reported systemic manifestations there was no evidence to address this question.

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?

Since no studies reported systemic manifestations there was no evidence to address this question.

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

All gaps listed here indicate could benefit from future research.

i. Systemic response for PUR as a material and for all devices included in this review. There was no included literature that reported on systemic response.
ii. Device failure as a function of biocompatibility or mechanical integrity. The most common reported outcome in the literature and surveillance data related wo
iii. Patient or material related factors for local response to PUR devices.
iv. Local response to PUR in ventricular assist devices and neuromodulatory devices. There was very little (and low quality) evidence for local response to these devices.

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 were selected by FDA based on current priority. For 2020, the following six materials were chosen:

1. Siloxane (Si)
2. Polypropylene (PP)
3. Polyether ether ketone (PEEK)
4. Poly(lactic-co-glycolic acid) (PLGA)
5. Polyurethane (PUR)
6. Polyethylene terephthalate (PET)

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 the material?
   - Over what time course does this local host response appear?
   - Can that response vary by location or type of tissue the device is implanted in or near?
2. Does the material elicit a persistent or exaggerated response that may lead to systemic signs or symptoms – beyond known direct toxicity problems?
   - What evidence exists to suggest or support this?
     - In-vivo/clinical studies/reports?
     - Bench or in-vitro studies?
   - What are the likely systemic manifestations?
   - What is the observed timeline(s) for the systemic manifestations?
   - 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/research are 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 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 non-clinical 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 date 2010 – 2020 and English as the publication language. ECRI and FDA agreed on appropriate host and material response search concepts as follows:

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

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

Search strategies were developed for each concept and combined using Boolean logic. Several search approaches were used for comprehensiveness. Strategies were developed for devices of interest as indicated by the 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 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 2020, 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 – Polyurethane

Full Name: Polyurethane

CAS Registry Number: 61789-63-7

Search Overview

The systematic review included clinical and engineering literature on biocompatibility (i.e., host response and material response) of polyurethane (PUR) used in medical devices. In addition to fundamental material biocompatibility, we focused on specific devices known to be made of polyurethane. 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 polyurethane provided by FDA to guide ECRI searches.

Regulatory Description	Pro Code	Class
Catheters made of PUR that reside in body > 24 hrs		
PICC		
Hemodialysis Catheters	MSD, PKI, NIF, NYU	II
Port Catheters		
Central Venous Catheters (CVC)		
Broviac Catheters		
Hickman Catheters		
Umbilical Artery Catheters	FOZ	
Ventricular Assist Devices		
Impella Catheters		
Intra-aortic Balloons/catheters		
Neurostimulation Devices	QLK, LGQ, GZF, GZB	II, III
Cardiovascular Pacemaker Electrodes	DTB, OJX, NVN, KFJ	III
Pacemaker Repair and Replacement Material		
Implanted electrical urinary/fecal continence devices	EZW	III

The Safety Brief summarizes the findings of the literature search on toxicity/biocompatibility of PUR. 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 PUR as a material as well as research on the various device categories.

Table 2: Summary of primary findings from our systematic review

Application: PUR as a material (2 human studies, 27 animal studies)
Local host responses/ Device events: Inflammatory response or foreign body reaction, granuloma, graft patency, graft rupture, graft degradation, occlusion, stent migration, thrombosis, fibrosis, adhesions, mesh exposure
Quality of evidence (local responses): Moderate for inflammatory response or foreign body reaction
Low for graft patency/occlusion
Very low for all other outcomes
Systemic responses: Not investigated
Quality of evidence (systemic responses): Very low (no evidence)

Application: Intravascular catheters (29 human studies, 1 animal study)
Local host responses/ Device events: Catheter dysfunction (including catheter fracture, catheter occlusion, catheter displacement or migration), thrombosis, phlebitis, erythema, pain, edema, hemorrhage, rupture, swelling
Quality of evidence (local responses): Moderate for catheter dysfunction, phlebitis, and thrombosis
Low for all other outcomes
Systemic responses: Not investigated
Quality of evidence (systemic responses): Very low (no evidence)

Application: Blood access devices (14 human studies)
Local host responses/ Device events: Catheter dysfunction (including catheter fracture, catheter occlusion, catheter displacement), thrombosis, pseudoaneurysm, bleeding, hematoma, stenosis, swelling, pain, erythema
Quality of evidence (local responses): Moderate for catheter dysfunction and thrombosis
Low for all other outcomes
Systemic responses: Not investigated
Quality of evidence (systemic responses): Very low (no evidence)

Application: Catheter securement devices (3 human studies)
Local host responses/ Device events: Catheter failure, dysfunction, dislodgement, thrombosis
Quality of evidence (local responses): Moderate
Systemic responses: Not investigated
Quality of evidence (systemic responses): Very low (no evidence)

Application: Cardiovascular pacemaker electrode (3 human studies)
Local host responses/ Device events: Lead failure, lead dislodgement, severe insulation damage
Quality of evidence (local responses): Low
Systemic responses: Not investigated
Quality of evidence (systemic responses): Very low (no evidence)

Application: Ventricular assist devices (1 human study, 1 animal study)
Local host responses/ device events: No local responses or events reported.
Quality of evidence (local responses): Very low
Systemic responses: Not investigated
Quality of evidence (systemic responses): Very low (no evidence)

Application: Neurostimulation devices (1 animal study)
Local host responses/ device events: Local immune response
Quality of evidence (local responses): Very low
Systemic responses: Not investigated
Quality of evidence (systemic responses): Very low (no evidence)

Application: Pacemaker repair or replacement material, implanted electrical urinary/fecal continence devices (no studies)
Local host responses/ device events: No evidence
Quality of evidence (local responses): Very low
Systemic responses: No evidence
Quality of evidence (systemic responses): Very low

PUR as a Material: 2 human studies (1 RCT,[1] 1 cohort study[2]), 27 animal studies (11 RCTs,[3,5,8,10,11,15,19,22,24,26,29] 18 observational studies[4,6,7,9,12-14,16-18,20,21,23,25,27,28]).

Local host responses (human studies): Both human studies reported local responses. The RCT compared PUR foam to control foam as part of a wound dressing. At 8 weeks, neither foam was associated with any observable local or systemic reaction, or signs of allergy/sensitivity. One controlled cohort study compared a PUR-covered Diamond stent (PCD) to 5 other stents for treatment of malignant distal biliary obstruction. The PCD had good patency, with much lower occlusion than an uncoated metal stent, and a low incidence of migration.

Local host responses (animal studies): All 27 animal studies reported local responses to PUR. Although the studies evaluated PUR in a variety of forms (coated stents, scaffolds, foams) introduced via different routes (subcutaneous implant, vaginal implant, blood vessel graft, intramuscular injection, oral gavage) for different medical purposes, almost all of the studies reported on local inflammatory responses or foreign body reactions. Most studies reported the inflammatory responses to PUR were mild, and 2 studies reported no inflammatory response or foreign body reaction. Five studies of PUR blood vessel grafts evaluated graft patency. In 1 study vascular graft patency was significantly higher for PUR compared to PTFE stents, and 2 other studies reported patency rates over 90% for PUR vascular and abdominal aortic grafts. However, 2 studies of femoral and carotid artery grafts respectively found that untreated PUR grafts had a very low patency rate at 1 to 6 months compared to PU grafts treated with heparin or vascular endothelial growth factor (VEGF). One study reported no maternal and developmental toxicity following exposure to PUR degradation products. Outcomes reported in a single study included thrombosis, graft rupture, granuloma, and mesh exposure. Overall, the animal studies measured adverse events occurring from 1 week to 6 months following contact with PUR, with most studies evaluating events within the first 3 months or less.

Systemic responses: We did not identify any human or animal studies investigating systemic responses to PUR as a material.

Overall quality of evidence: A large number of animal studies (RCTs and observational designs) identified mild inflammatory or foreign body response as the most common local response to PUR. Because these are indirect evidence with respect to humans, the quality of evidence for these responses is moderate. The evidence for graft patency/occlusion showed inconsistent findings and the majority of evidence was from animal studies, so the quality of evidence for graft patency/occlusion is low. For all other outcomes (including systemic responses) the strength of evidence is very low.

Intravascular Catheters: 29 human studies (2 systematic reviews,[31,49] 7 RCTs,[37,38,40,52,54,57,58] 20 observational studies[30,32-36,39,41-48,50,51,53.55,56]), 1 animal RCT.[59]

Local host responses (human studies): Events reported in the systematic reviews (which represented multiple individual studies) and/or several individual studies include phlebitis, catheter dysfunction (including breakage, occlusion, and displacement), and thrombosis. A systematic review[31] of 35 studies with 15,791 total patients receiving peripheral intravenous catheters reported a lower incidence of infusion phlebitis for PUR Vialon catheters (26.5%) compared to PTFE Teflon catheters (33%) during mean follow-up times ranging from 1.5 to 12 days. Another systematic review[49] of 9 studies evaluating peripherally-inserted central catheters (PICC) reported a higher rate of phlebitis for PUR catheters (15%) compared to silicone catheters (8.3%)(follow-up times not reported). This contrasts with a separate RCT[58] that reported a lower rate of phlebitis with PUR PICCs (11.6%) than silicone PICCs (23.2%) over a mean contact time of 28.9 days. One cohort study[45] reported that PUR peripheral intravenous catheters had a significantly lower rate of phelebitis (17%) than Teflon catheters (37%) over a median contact time of 50 hours. PUR catheters were also associated with significantly lower rates of erythema and pain. 1 RCT[38] reported that PUR PICCs had a significantly lower rate of catheter-related thrombosis (8.7%) compared to external, non-tunneled heparin-coated Vialon central venous catheters (25%) over a median follow-up of 30 days. One cohort study[53] comparing aromatic versus aliphatic PUR subclavian central venous catheters reported a higher occlusion rate with aromatic (18%) than aliphatic (11%) catheters over a median contact time of 13 days. Another cohort study[56] reported that breakage was significantly lower with PUR PICCs (0%) than silicone PICCs (8%) over a mean dwell time of 78 days. A cohort study[30] reported a higher rate of catheter-related thrombosis (CRT) with PUR midline catheters (30%) compared to polyethylene long peripheral catheters (10% to 12.5%) over a mean contact time of 48 to 153 days. Another cohort study[33] reported a lower rate of catheter failure with PUR Surflo V3 catheters compared to PTFE Teflon catheters. Finally, a cohort study[36] reported that PUR PICCs had significantly higher rates of occlusion, dislodgement, and stenosis compared to tunneled silicone Broviacs catheters over a mean follow-up of 342 days; the PUR PICCs also had significantly lower rates of breakage compared to silicone Broviacs catheters and tunneled silicone PICCs. Other events reported in a single or few studies include edema, hemorrhage, rupture, and swelling.

Systemic responses (human studies): We did not identify any studies investigating systemic responses to PUR intravascular catheters.

Overall quality of evidence: Several studies (including systematic reviews and RCTs) reported the following events: phlebitis, catheter dysfunction (including breakage, occlusion, and displacement), and thrombosis. The evidence that these events occur with PUR catheter use is moderate. All other outcomes were reported in relatively few studies, so the quality of evidence for other outcomes is low. Since no studies investigated systemic responses, the quality of evidence for systemic responses is very low.

Blood Access Devices: 14 human studies (1 systematic review,[67] 2 RCTs,[66,69] 11 observational studies[60-66,68,70-73]).

Local host responses (human studies): Catheter dysfunction (including fracture, displacement and occlusion) was the most commonly reported adverse event. Thrombosis (often the cause of catheter occlusion) was also reported in several studies. One RCT[69] reported that standard double lumen (sDLC) PUR catheters had a higher rate of catheter dysfunction (measured after 3 days of continuous renal replacement therapy) than surface-modified DLC catheters (14% vs 5%), as well as a higher rate of thrombotic events. One systematic review[67] reported a higher rate of catheter obstruction with the PUR Port-a-cath catheter (9.2%) versus the PUR Chemosite catheter (5.1%) in 1 RCT with a mean follow-up of 29.5 months. Another RCT[66] reported no significant differences in catheter dysfunction or thrombotic occlusions between 2 different PUR catheters (LifeCath Twin and TesioCath) over a 12-month period. Four controlled cohort studies compared an implantable venous access port (IVAP) with a PUR catheter versus IVAP with a silicone catheter. One study reported no difference in complications between PU and silicone catheters, 1 study reported a higher catheter occlusion rate and overall complication rate for silicone catheters, 2 studies reported higher catheter fracture rates for silicone catheters, and 1 study reported higher rates of catheter tip thrombosis and overall complications for PUR catheters. One study comparing PUR catheters to PTFE catheters reported a slightly higher rate of thrombosis in PUR catheters, but there were too few events for a statistically significant between-group difference. The follow-up period in these studies ranged from 1 month to 3 years. Other events reported in one or more studies included bleeding, hematoma, stenosis, swelling, pain, erythema, and pseudoaneurysm.

Systemic responses (human studies): We did not identify any studies investigating systemic responses to PUR blood access devices.

Overall quality of evidence: Several studies provided evidence on catheter dysfunction and thrombosis related to PUR blood access devices, but most of the evidence was from observational studies and there was minor inconsistency in the findings of studies comparing PUR catheters to other catheter types. Therefore, the quality of evidence for catheter dysfunction and thrombosis is moderate. For other outcomes reported in fewer studies the quality of evidence is low. Since no studies investigated systemic responses, the quality of evidence for systemic responses is very low.

Catheter Securement: 3 human studies (1 systematic review,[74] 1 network meta analysis,[75] and 1 controlled cohort study[76]). For further information, see Table 6 in Appendix D.

Local host responses (human studies): A 2020 systematic review[74] examined various dressings and securement devices for catheter stabilization in five RCTs. Four RCTs reporting outcomes of interest enrolled 123 to 330 adults. No information was provided on duration, dose, or frequency/duration of dressings and devices.

Of the four relevant RCTs, two RCTs compared bordered PUR dressing (BPD), standard PUR dressing (SPD), tissue adhesive (TA) with SPD, and sutureless securement devices (SSDs) with SPD. Both RCTs reported peripheral arterial catheter (PAC) failure as a composite outcome with components including complete dislodgement, occlusion, and pain. Both studies indicated higher catheter failure with SPD vs. BPD (1 RCT: 21% SPD, 5% BPD, 11% TA, 16% SSD; p=0.03 SPD vs. BPD)(1 RCT: 20% SPD, 13.3% BPD, 6.3% TA with SPD, 16.1% SSD with SPD). A third RCT also reporting PAC failure, compared a PUR adhesive keyhole dressing (Veni-Gard) with Veni-Gard plus OpSite, a PUR semipermeable transparent dressing. Authors noted higher failure with Veni-Gard (60% Veni-Gard, 40% Veni-Gard plus OpSite) with similar incidence of occlusion (50%). The fourth RCT (the ADVANCED study) comparing PUR transparent dressings with new-generation dressings indicated dysfunction incidence rates of 12.9 per 1,000 catheter-days.

A 2019 network meta analysis[75] examined 13 antimicrobial dressings including standard PUR dressing (SPU) and bordered PUR dressing (BPU). A minimum duration of catheter placement of at least 48 hours was required. Eight RCTs reporting catheter failure indicated statistically significant reductions with SSD vs. other dressings (Odds ratio 0.35, 95% CI: 0.14 to 0.89). Lowest to highest incidence of catheter failure was reported as follows: SSD, transparent dressing, SPU, SSD plus SPU, chlorhexidine gluconate-impregnated dressing, suture plus adherent dressing, TA plus SPU, BPU, SPU plus BPU, TA, suture plus BPU, integrated securement dressing, and sterile dry gauze.

Lastly, one controlled cohort study[76] examined 95 PUR central venous catheters (CVCs) versus 78 silicone CVCs with or without use of subcutaneously anchored securement (SAS) in pediatric patients. Mean dwell time of catheters was 188 days. PUR made up 54.9% of all catheters; 42% of Group A (no use of SAS), and 86% of Group B (use of SAS). Complications included 27 dislodgements (25 in Group A, 2 in Group B), 4 thrombosis (3 in Group A, 1 in Group B), and 6 malfunctions (5 in Group A, 1 in Group B).

Systemic responses (human studies): We did not identify any studies investigating systemic responses to PUR catheter securement devices.

Overall quality of evidence: Systematic reviews of RCTs provided evidence of catheter dysfunction/failure that can occur with PU catheter securement devices and other catheter securement devices. Since some of the comparisons are indirect in the network meta-analysis, the quality of evidence regarding the ranking of catheter securement devices is moderate. Since no studies investigated systemic responses, the quality of evidence for systemic responses is very low.

Cardiovascular Permanent or Temporary Pacemaker Electrode: 3 human studies (1 retrospective cohort,[77] 1 prospective cohort,[78] 1 case series[79]).

Local host responses: All three human studies reported local responses or events, primarily lead failure and lead dislodgement (2 studies). Lead failure was defined as any malfunction that necessitates a replacement. Causes for lead failures were varied, and not systematically examined or compared in either study. Overall failure rates were low, but not insignificant. PU80A showed on average a remarkably higher failure rate than PU55D, silicone-

polyurethane copolymer, and silicone insulation. One study suggested that lead failure is related to the model of the electrical lead, and not specifically related to the insulation material. The case series also reported severe insulation damage for all polyurethane-coated leads, which exceeded the rate of damage for silicone-coated leads. These events occurred over a mean follow-up ranging from 25.7 months to 82.2 months across studies.

Systemic responses: We did not identify any studies investigating systemic responses to PUR cardiovascular pacemaker electrodes.

Overall quality of evidence: The evidence supporting local responses to pacemaker insulation was inconsistent. Not every material used in the study was the exact same and different studies reported different lead failure rates. In addition, all three studies were observational and the quality of evidence was therefore low. The quality of evidence for systemic responses was very low (due to no evidence).

Ventricular Assist Devices: 1 human study (case series[80]) and 1 animal study (single case[81]).

Local host responses: Both studies reported no local response related to PUR.

Systemic responses: We did not identify any studies investigating systemic responses to PUR ventricular assist devices.

Overall quality of evidence: The evidence supporting local response to PUR ventricular assist devices is extremely poor with extremely low sample sizes in each study, both observational in nature. Furthermore, PUR is only tangentially related to the purpose of the studies. The quality of evidence was therefore very low. The quality of evidence for systemic responses was very low (due to no evidence).

Neurostimulation Devices: 1 animal study (comparative observational study[82]).

Local host responses: One animal study suggests a polyethylene glycol containing PUR coating for neural electrodes had reduced tissue immune response and greater survivability for surrounding neurons compared to an uncoated control.

Systemic responses: We did not identify any studies investigating systemic responses to PUR neurostimulation devices.

Overall quality of evidence: The evidence supporting local response of PUR neurostimulation devices consists of a single observational animal study with a low sample size, so the quality of evidence is therefore very low. The quality of evidence for systemic responses is also very low (due to no evidence).

Pacemaker Repair or Replacement Material: We did not identify any human or animal studies that evaluated these devices.

Implanted Electrical Urinary/Fecal Continence Devices: We did not identify any human or animal studies that evaluated these devices.

ECRI Surveillance Data

The most common complication reported within PUR surveillance data was related to device malfunction or failure. It is unclear in the data if failure was material response due to insufficient biocompatibility or related to mechanical integrity and use of the device.

Patient Safety Organization

Search Results: ECRI PSO identified 5,247 reports that involved PUR materials that occurred between 6/2005 through 5/2020. 1529 of these involved complications. The top 5 complications included: 1) Device malfunction/failure - 549 (35.9%), 2) Occlusion - 391 (25.6%), 3) Infection - 150 (9.8%), 4) Migration - 138 (9.0%) and 5) Bleeding - 66 (4.3%). Harm occurred in 24.5% of the events. 6 of the 11 reported deaths were associated with the Impella device.

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

Table 3: Complications in polyurethane-related PSO event reports

Complication	Broviac	Dialysis	Hickman	Impella	Intra-aortic	Pacer	PICC	PTCA	UAC	VAD	Total
Device malfunction/failure	95	11	34	31	47	1	286	9	9	26	549
Occlusion	7	12					372				391
Infection	19	5	38			19	57	2	1	9	150
Migration	2	8	3	17	1		102		4	1	138
Bleeding	11		10	21	2			9	7	6	66
Venous Thromboembolism		1		6	1		47	2	2	2	61
Device fracture	14	2	2	5		2	2			2	29
Clinical Manifestations	3		6	6			1	10		2	28
Iatrogenic Injury	2			8	2	1		10		2	25
Dissection								19			19
Hematoma	1			9				8			18
Limb ischemia	3			11						3	17
Cardiac Arrest	1			5				3			9
Lead issue						7					7
Skin injury/issue	1			4				1			6
Prolonged fluoro time								4			4
Infiltrate/extravasation	3										3
Pain			3								3
Pseudoaneurysm								3			3
Compartment Syndrome				1				1			2
Inflammation/Irritation			1								1
Total	**162**	**39**	**97**	**124**	**53**	**30**	**867**	**81**	**23**	**53**	**1529**

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

Cate-gory	Sev-erity	Broviac	Dialysis	Hickman	Impella	Intra-aortic	Pacer	PICC	PTCA	UAC	VAD	Total
A	No Error	1	1	1	2	--	--	20	3	1	3	32
B1	Error, No Harm	--	--	--	--	--	--	2	--	--	--	2
B2	Error, No Harm	27	1	3	5	--	--	19	--	1	2	58
C	Error, No Harm	35	8	17	13	7	4	228	4	3	5	324
D	Error, No Harm	20	10	25	23	18	5	224	18	8	13	364
E	Error, Harm	30	9	20	30	8	9	142	29	2	9	288
F	Error, Harm	2	3	16	8	1	3	13	7	1	5	59
G	Error, Harm	2	1	--	2	2		3	2	--	1	13
H	Error, Harm	--	--	--	1	--	--	1	--	--	1	3
I	Error, Death	--	--	2	6	1	--	--	1	--	1	11
NULL		45	6	13	34	16	9	215	17	7	13	375
Total		162	39	97	124	53	30	867	81	23	53	1529

**Harm score was not reported*

Accident Investigations

Search Criteria: PICC, Hemodialysis, Port, Central Venous Catheter, CVC, Broviac, Hickman, Umbilical Catheter, Impella, Intra-aortic Balloon, IAB, Defibrillator Lead, and Pacemaker Lead. Investigation files from 2008-2020 were searched to recover cases pertaining to the polyurethane device categories listed above.

Search Results: Eight investigations were recovered and are summarized in Table 5.

These investigations are redacted and included in Appendix F.

Table 5: Accident investigations of patient incidents involving polyurethane.

Device Type	# Investigations	Reported Problem and Findings
Intra-aortic Balloon Catheter	3	Leak, Perforation, Thrombosis, Material Defect
Dilation and Percutaneous Transluminal Valvoplaty Catheter	1	Failure to Deflate
Umbilical Vessel Catheter	1	Leak
Implanted Pacemaker Lead	1	Fracture
VAD Catheter	1	Entrapment
Epidural Catheter	1	Broke into 2 pieces

ECRI Problem Reports

Search Criteria: Broviac, Hickman, Leonard, CVC, Impella, Heartmate, LVAD, left ventricular assist, VAD, Hemodialysis, PICC, umbilical, catheter, coronary stent.

Search Results: The search returned 198 reports submitted by ECRI members.

Key Issues: The reports detail devices breaking, leaking, ballooning, not functioning as intended, stop functioning, and patient symptoms of shortness of breath, respiratory distress, sneezing coughing, agitation, redness of body, legs, face and edema of face, eyes, lips.

Safety Concerns: The reports detailed delayed procedures, additional imaging, additional medications, additional surgeries, prolonged hospital stay, and prolonged surgeries.

All problems reports are redacted and included in Appendix F.

Table 6: ECRI Problem Report Summary

Device Type	# Problem Reports	Reported Problem (number of problem reports)
Catheter, intravascular, therapeutic, long-term greater than 30 days (LJS)	160	Devices leaking, breaking, breaking off in patient, rupturing, ballooning Patient symptoms of infection, shortness of breath, respiratory distress, sneezing, coughing, agitation, redness of body, legs, face, edema of face, eyes, lips.
Ventricular Assist Device (OJE)	4	Stopped functioning, flow inadequate, components separated
Catheter, intravascular, therapeutic, short-term less than 30 days(FOZ)	4	Leaking, broke

Device Type	# Problem Reports	Reported Problem (number of problem reports)
Catheter, hemodialysis, implanted (MSD)	1	Broke
Right ventricular bypass (assist) device(OJE)	1	Broke during removal
PICC (unknown)	17	Leaking, Broke , failure to flush
Coronary drug-eluting stent(NIQ)	5	Balloon would not deflate, Balloon disengaged, tip broke
IAB catheter(DSP)	5	Balloon rupture, catheter kink, catheter would not advance

Alerts

Search Criteria: See excel sheet of search terms

Search Results: The search returned 304 manufacturer or regulatory agencies issued alerts describing problems including labeling, manufacturing, sterility, IFU updates, failure to meet validated specifications, inclusion of incorrect components, battery performance and charging, disconnection, fracture, leakage, software calculation issues, embolization risk, and RF interference, summarized in Table 7.

Table 7: Summary of regulatory and manufacturer alerts

Device Type	# Alerts	Problems
Stimulator, Electrical, Implantable, For Incontinence (EZW)	7 Manufacturer-issued	• Unexpected stim increase • Sterility compromised • Mislabeling • Software issue • Cybersecurity vulnerability
Catheter, Hemodialysis, Implanted (MSD)	7 Manufacturer-issued	• Fracture/Leakage • Detachment • Sterility compromised • Mislabeling • Distribution beyond expiration • Inadequate weld
Catheter, Hemodialysis,	2 Manufacturer-issued	• Bent tip • Failure to meet validated specs

Device Type	# Alerts	Problems
Implanted (MSD, NYU 'coated')		
Catheter, Hemodialysis, Implanted, Coated (NYU)	1 Manufacturer-issued	• Incorrect component
Catheter, Hemodialysis , Implanted; Catheter, Intravascular, Therapeutic (MSD, LJS, FOZ)	1 Manufacturer-issued	• Incorrect priming value on catheter and in IFU
Permanent Pacemaker Electrode (DTB)	3 Manufacturer-issued	• Mislabeling • Sterility compromised • Processed outside validated specs
Drug Eluting Permanent LV Pacemaker Electrode (OJX)	3 Manufacturer-issued	• Out of spec weld • Battery performance • Abrasion of silicone insulation
Drug Eluting Permanent RV or RA Pacemaker Electrodes (NVN)	14 Manufacturer-issued	• PLM Updated • PUR boot not securely connected • Asynchronous rhythms • Accelerated battery depletion • Intermittent over-sensing • Configuration not FDA-approved • Mislabeling • Circuit error • Pacing doesn't match setting • Inappropriately triggered indicators • Inhibited pacing or device reset
Catheter, Intravascular Occluding, Temporary (MJN)	17 Manufacturer-issued	• Customer confusion over removal • Balloon deflation unexpected/difficult • Damage after insertion • Fracture • Sterility compromised • Mislabeling • Packaging issue • Incorrect IFU • Blockage

Device Type	# Alerts	Problems
Catheter, Intravascular, Diagnostic (DQO)	25 Manufacturer-issued	• Sterility compromised • Embolization risk • Mislabeling • Foreign material • Brittle/degrading material • Tip split/separation • Failure to meet validated parameters • Inability to calibrate • Fracture during use
Catheter, Intravascular Occluding, Temporary; Catheter, Intravascular, Diagnostic (MJN, DQO)	1 Manufacturer-issued	• Sterility compromised
Catheter, Intravascular, Diagnostic; Optical Coherence Tomography, Intravascular Catheter (DQO, ORD)	1 Manufacturer-issued	• IFU missing information
Catheter, Intravascular, Diagnostic; Catheter, Ultrasound, Intravascular (DQO, OBJ)	6 Manufacturer-issued	• Updated PM interval • Software/calculation issues • Ultrasound display issues
Catheter, Intravascular, Therapeutic, Long-Term (LJS)	30 Manufacturer-issued	• Fracture/leakage • Sterility compromised • Mislabeling • IFU updated/missing information • Difficulty maintain secure connection • Trays do not contain iodine • Released subject to importation refusal • Pin holes • Kit contains incorrect component
Catheter, Intravascular, Therapeutic (LJS, FOZ)	10 Manufacturer-issued	• Mislabeling • Packaging changes • Sterility compromised • Contain recalled product • Detachment • Increased hemolyzed blood samples

Device Type	# Alerts	Problems
Catheter, Intravascular, Therapeutic, Short-Term	25 Manufacturer-issued	• Sterility compromised • Needle retraction issue/sharps injury risk • Mislabeling • Discontinued product • Fracture/leakage/puncture • Supply interruption • Packaging issue • Cannot aspirate • Canister burst • Embolization risk • Failure to meet validated specs/cGMP complicate requirements
Catheter, Ultrasound, Intravascular (OBJ)	34 Manufacturer-issued	• Imaging error • Loss of system control/data loss • Incorrectly processed catheter • Brittle component/detachment • Catheters kinking • Catheters entangled with stents • Atrial perforation and AV node block • EM interference • Software/calculation issue • Cybersecurity vulnerability • Patient identification error • Hardware issue • Transducer overheating • Noncompliance with IEC standards
Catheter, Ultrasound, Intravascular; Reprocessed Intravascular Ultrasound Catheter (OBJ, OWQ)	1 Manufacturer-issued	• Software issue
Port & Catheter, Implanted, Subcutaneous, Intravascular (LJT)	37 Manufacturer-issued	• Mislabeling • Fracture/Leakage • Will not allow guidewire passage • Connectors will not remain closed • Sterility compromised • Catheter insertion issues • Clinicians unable to place ports • Incorrect components • Catheter disconnection • Catheter deterioration • Incorrect IFU • Needle occlusion

Device Type	# Alerts	Problems
Reprocessed Intravascular Ultrasound Catheter (OWQ)	1 Manufacturer-issued	• Mislabeling
Stimulator, Spinal-Cord, totally Implanted for Pain Relief (LGW)	26 Manufacturer-issued	• Heating during charging/burns from charging • Charging issues • Low impedance • Early triggering • RF interference • Over-stimulation/loss of stimulation • Failure to meet validated specs • Neurological deficit • Mislabeling/updated labeling • Corrupted data • Manufacturing defect • Decreased battery longevity • External device proximity issues
Stimulator, Peripheral Nerve, Implanted (Pain Relief) (GZF)	2 Manufacturer-issued	• Software issues • Incorrect IFU
Ventricular (Assist) Bypass; Right Ventricular Bypass (Assist) Device (DSQ, OJE)	4 Manufacturer-issued	• EMI/RF interference • Cable damage
Ventricular (Assist) Bypass; Pediatric Ventricular Assist Device (DSQ, PCK)	1 Manufacturer-issued	• Membrane disruption
Ventricular (Assist) Bypass (DSQ)	1 FDA Warning Notification 39 Manufacturer-issued	• Components dislodged or disconnected • Fracture/leakage/kinking/bending • Missing power cord • Circuit/controller/connector issues • Fluid ingress • Power switching • Persistent, unexpected or missing alarms • New version/system updates • Contaminated driveline • High rate of stroke/bleeding • Connector pin retraction • Susceptibility to electrostatic discharge • Unexpected discoloration/wear • Premature battery failure • Risk of user error (resulting in death) • Particulate in patient during surgery • Missing screws • Stopping without warning

Device Type	# Alerts	Problems
Right Ventricular Bypass (Assist) Device (OJE)	3 FDA Warning Notification	• FDA issues EUA • Higher-than-anticipated mortality rate

Potential Gaps

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

Overall, the literature for PUR generally lacked data on patient-related or material-related factors that influence the likelihood and/or severity of sustained, exaggerated systemic responses. There were no included studies on any PUR devices that reported on systemic responses, indicating areas of potential future research.

ECRI surveillance data largely consisted of device related failures or malfunctions without further indication of causation. In general, material failures could be an indication of insufficient biocompatibility.

PUR as a Material: A large number of animal studies identified mild inflammatory or foreign body response as the most common local response to PUR; however, there were no identified studies investigating systemic responses to PUR as a material. This indicates a potential area of further research.

Intravascular Catheters: There is a moderate quality of evidence with regard to phlebitis, catheter dysfunction (including breakage, occlusion, and displacement), and thrombosis associated with PUR intravascular catheters. In addition, device malfunction or breaking was the leading complication in our surveillance data. It is not readily apparent whether this is a function of biocompatibility or device use. This indicates an area of potential future research.

Blood Access Devices: Several studies provided evidence on catheter dysfunction and thrombosis related to PUR blood access devices, but most of the evidence was from observational studies and there was minor inconsistency in the findings of studies comparing PUR catheters to other catheter types. The quality of evidence was moderate for these studies, but additional research here may strenghten these findings.

Catheter Securement: There were no clear gaps regarding the device malfunctions reported in the literature.

Cardiovascular Permanent or Temporary Pacemaker Electrode: The evidence supporting local responses to pacemaker insulation was inconsistent and associated with low quality of evidcne. This indicates that future research would be beneficial.

Ventricular Assist Devices: The evidence supporting local response to PUR ventricular assist devices is extremely poor with extremely low sample sizes in each study, both observational in nature. Furthermore, PUR is only tangentially related to the purpose of the studies. The quality of evidence was therefore very low and suggests an area of future research.

Neurostimulation Devices: The evidence supporting local response of PUR neurostimulation devices consists of a single observational animal study with a low sample size. This suggests an area of future research.

Pacemaker Repair or Replacement Material: We did not identify any human or animal studies that evaluated these devices.

Implanted Electrical Urinary/Fecal Continence Devices: We did not identify any human or animal studies that evaluated these devices.

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

Inclusion Criteria

1. English language publication
2. Published between January 2010 and September 2020
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 polyurethanes or priority devices that include this material

Exclusion Criteria

1. Foreign language publication
2. Published before January 2010
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 (human and animal) providing relevant data.
3. **Consistency of data** – are the findings consistent across studies that report relevant data?
4. **Magnitude of effect** – in human and animal studies, 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)? Animal studies are indirect but may provide the best evidence for the material itself.
6. Is there evidence of a **dose response or time response** (e.g. adverse effects increase with longer exposure time)?

Appendix B. Search Summary

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

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

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

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

Material

Set Number	Concept	Search statement
1	**Polyurethane**	'polyurethan'/exp OR 'polyurethan'/syn OR 'polyetherurethan'/exp OR 'polyetherurethan'/syn OR 'polyurethan foam'/exp OR polyurethan*:ti,ab,de,dn,kw OR polyetherurethan*:ti,ab,de,dn,kw OR 'polyether urethan*':ti,ab,de,dn,kw OR 'poly urethan*':ti,ab,de,dn,kw OR 'poly etherurethan*':ti,ab,de,dn,kw OR ((urethan* OR 'pu' OR 'pur' OR 'peur') NEAR/3 (polymer* OR copolymer* OR blend* OR elastomer* OR polyester* OR polyether* OR compound* OR composite*))
2		('55d pu' OR adiprene OR bayflex OR carbothan OR chronoflex OR crisvon* OR ducor OR elastogran* OR elastollan* OR elasthan OR elastothan* OR estane OR hydran* OR isoplast* OR mitrathan* OR neuthan* OR pellethan* OR quadraplast OR quadrathan* OR 'specfil' OR specflex OR tecoflex OR tecothan* OR tesio OR texin OR vialon*):ti,ab,de,dn,kw

3		'polycarbonate urethane*' OR 'poly carbonate urethane*' OR 'poly ether urethane*' OR corethane? OR bionate? OR carbothane? OR microthane?
4	**Combine sets**	**#1 OR #2 OR #3**
5	Limit by language and publication date	#4 AND [english]/lim AND [2010–2020]/py
6	Limit by publication type	#5 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)
7		'biocompatibility'/de OR biocompat* OR tribolog* OR 'bio compat*' OR 'biological* compat*' OR 'biological* evaluation'
8		'degradation'/exp OR degradation OR degrad* OR split OR splitting OR split* OR wear OR deteriorat* OR atroph* OR migrat* OR movement OR shift* OR transfer* OR 'delamination'/exp OR delamina* OR leach* OR filtrate OR filter* OR seep* OR evaginat* OR subsidence
9		Leachable* OR extractable*
10		(swell* OR shrink* OR contract* OR stretch* OR retract* OR extension OR extend* OR deform* OR creep OR plasticity OR degrad* OR disintegrat*) NEAR/3 (implant* OR material OR catheter* OR picc* OR pivc* OR line OR lines OR lumen OR device* OR electrod* OR lead OR leads OR neurostimulator* OR stimulator* OR bioprosthes* OR prosthes*)) OR 'device failure'/exp OR 'device safety'/exp OR 'catheter breakage'/exp OR 'catheter fracture'/exp
11		‘mechanics’/exp [see Emtree explosions section at the end of the strategy]
12		‘device material’/exp/mj
13		‘Biomedical and dental materials’/exp/mj
14	**Combine sets**	**#7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13**

Host Response

Set Number	Concept	Search statement
15		Host NEAR/2 (reaction* OR response*)
16		‘toxicity’/exp OR toxic*:ti OR cytotox* OR teratogenic* OR genotox* ‘carcinogenicity’/exp OR carcinogen*:ti

17		'blood vessel occlusion'/exp OR occlusion OR occlud* OR (fibrin NEAR/2 (sheath OR sleeve OR tail))
18		‘immune response’/exp OR ‘immunity’/exp/mj OR ‘hypersensitivity’/exp OR ‘immunopathology’/exp/mj
19		Immun*:ti OR autoimmun*:ti OR hypersens*:ti
20		'inflammation'/exp OR inflamm*:ti OR 'phlebitis'/exp OR 'phlebitis'/syn OR phlebitis OR thrombophlebitis
21		‘foreign body reaction’ OR granuloma*
22		('adhesion'/exp OR 'tissue adhesion'/exp OR 'biomechanics'/exp OR biocompat*)
23		'bacterium adherence'/exp OR 'biofilm'/exp OR biofilm
24		'calcification'/exp OR 'catheter thrombosis'/exp
25		(protrude* OR protrus*)
26		Migrat* OR migration OR evaginat* OR subsidence
27	**Combine sets**	**#15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26**

Devices

Set Number	**Concept**	**Search statement**
28	Catheters	'catheterization'/exp OR 'catheters and tubes'/exp OR 'vascular access'/exp OR 'cannula'/exp
29		tunnel* NEAR/5 (venous OR intravenous OR 'iv' OR arterial OR vascular OR intravascular OR central OR indwelling OR 'in-dwelling' OR peripheral* OR hemodialysis)
30		device* NEAR/5 (venous OR intravenous OR 'iv' OR arterial OR vascular OR intravascular OR central OR indwelling OR 'in-dwelling' OR peripheral* OR hemodialysis OR infusion)

31		(cvc? OR picc? OR pivc? OR jicc? OR sicc? OR sbcc? OR pvc? OR ivi?):ti,ab,kw
32		catheter* OR cath? OR port? OR cannula? OR hub?
33	Combine sets	#28 OR #29 OR #30 OR #31 OR #32
34	VADs	‘heart assist device'/exp OR 'assisted circulation'/exp
35		((heart OR ventric* OR vascular* OR circulatory) NEAR/3 assist*) OR (artificial NEAR/3 ventricl*) OR hvad? OR lvas OR lvad? OR vad? OR vas OR bivad? OR pvad? OR rvad?
36		heartmate* OR heartware* OR excor OR 'berlin heart' OR novacor OR impella OR centrimag
37	Combine sets	#34 OR #35 OR #36
38	**Combine sets**	**#33 OR #37**
39	**PU AND Material Response**	**#6 AND #14**
40	**PU AND Host Response**	**#6 AND #27**
41	**Devices AND Material Response**	**#38 AND #14**
42	**Devices AND Host Response**	**#38 AND #27**
43	**Combine all**	**#39 OR #40 OR #41 OR #42**

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

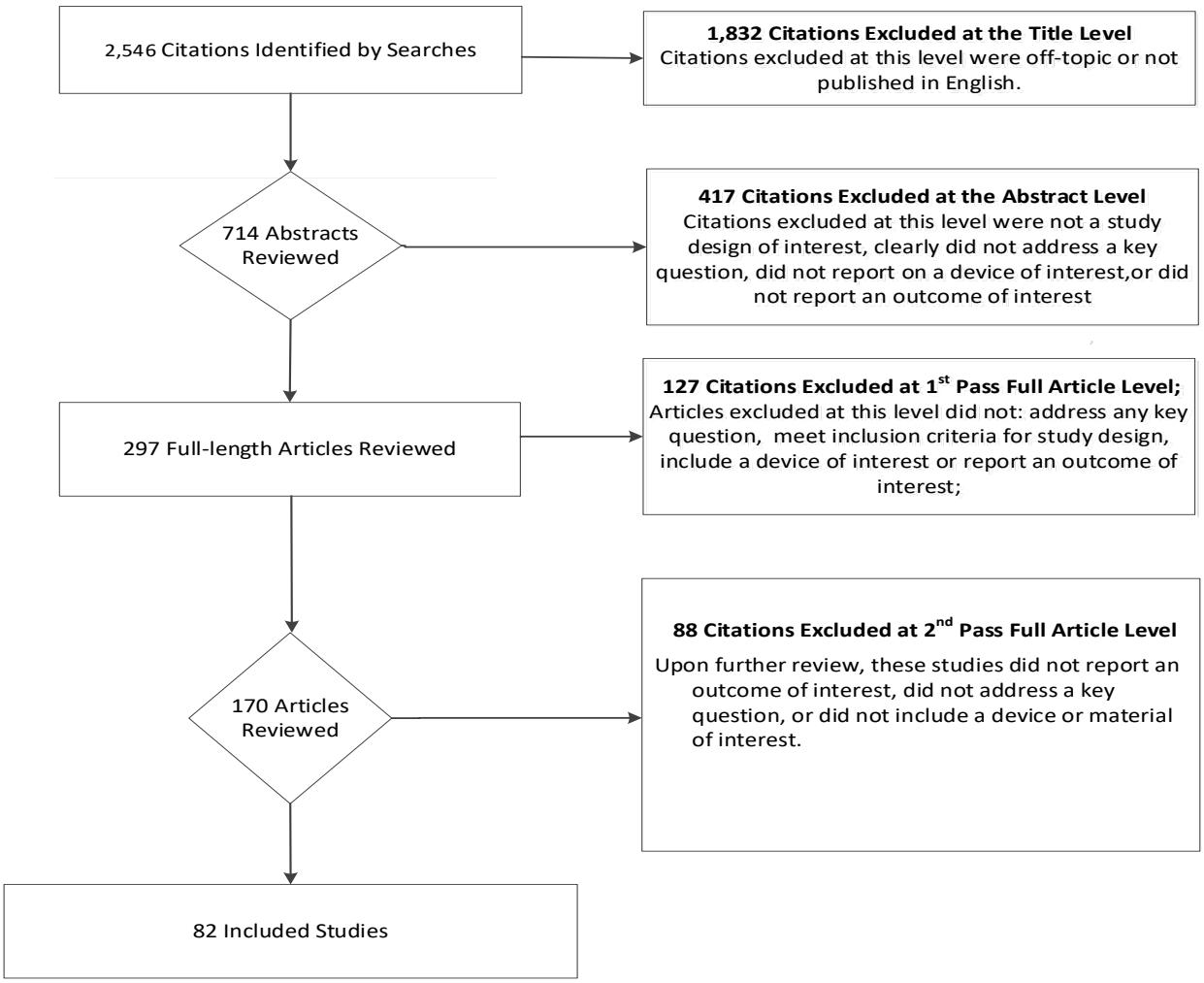
                        - Thyroid weight
                        - Uterus weight
                    - Seed weight
                    - Tablet weight
                    - Thrombus weight
            - Weightlessness
        - Hydrodynamics
            - Hypertonic solution
            - Hypotonic solution
            - Isotonic 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 8: PUR as a Material – Health Effect (In Vivo) Human Studies

Source citation: Wagstaff et al. 2014[1]

Study Design: RCT
Device Material: PU foam (NovoPore) vs control foam (Granufoam)
Contact Duration: 8 weeks
Dose: Cut to size of debrided wound
Frequency/ Duration: Dressings changed 3 x per week
Response: Local reaction or allergy/sensitivity (none observed)
Patient characteristics (gender, mean age): NR.
Number per group: 9.
Observed adverse effects: Neither foam was associated with any observable local or systemic reaction, or signs of allergy/sensitivity.
Timing of adverse effects: 8 weeks.
Factors that predict response: NA

Source citation: Isayama et al. 2011[2]

Study Design: Controlled cohort study
Device Material: Polyurethane-covered Diamond stent (PCD) (Microvasive/Boston Scientific, Natick, MA, USA), partially silicone-covered WALLSTENT (SCW), ComVi stent (Taewoong Medical Device, Seoul, Korea), and UMS.
Contact Duration: Median 600 to 1300 days
Dose: NR
Frequency/ Duration: NR
Response: Stent occlusion, Stent migration
Patient characteristics (gender, mean age): NR.
Number per group: PCD 55, SCW 151, ComVi 116, Viabil 40, UMS 106.
Observed adverse effects: Occlusion: PCD 10 (18%), SCW 32 (21%), ComVi 40 (34%), Viabil 4 (10%), UMS 51 (48%). Migration: PCD 5 (9%), SCW 23 (15%), ComVi 13 (11%), Viabil 0, UMS 1 (1%).
Timing of adverse effects: 1 to 600 days.
Factors that predict response: NR.
NA: not applicable; NR:not reported; PU: polyurethane; RCT: randomized controlled trial

Table 9: PUR as a Material – Health Effect (In Vivo) Animal Studies

Source citation: Eilenberg et al. 2020[3]

Study Design: RCT
Device or Material: dPCU, ePTFE conduits
Route: Infrarenal abdominal aorta implants
Dose: NR
Frequency/ Duration: Single administration
Response: Occlusion, Fatal thrombosis
Species (strain): Rat (Sprague-Dawley).
Gender: Male.

Number per group: 28
Observations on adverse effects (brief): Occlusion occurred after 100 days in 1 dPCU animal because of intimal hyperplasia, and 2 rats died after early thrombosis within the first week in the ePTFE group. Therefore, patency was 92.9% for dPCU and ePTFE according to Kaplan-Meier estimates.
Timing of adverse effects: See above
Factors that predict response: NR

Source citation: Feng et al. 2020[4]

Study Design: Case series
Device or Material: Waterborne PU (WBPU)
Route: Subcutaneous implant (in back)
Dose: 1 x 1 cm membrane
Frequency/ Duration: Single administration
Response: Inflammatory response
Species (strain): Rat (Sprague Dawley).
Gender: Male.
Number per group: 4
Observations on adverse effects (brief): Mild inflammatory response at 1 week which was reduced by 3 weeks.
Timing of adverse effects: 1 and 3 weeks
Factors that predict response: NR.

Source citation: Hympanova et al. 2020[5]

Study Design: RCT
Device or Material: Electrospun PU, PP (Restorelle), or electrospun UPy-PC mesh
Route: Vaginal prolapse repair implant
Dose: 35 x 35 mm implant
Frequency/ Duration: Single administration
Response: Inflammatory response
Species (strain): Sheep (Lakens).
Gender: Female.
Number per group: 6 (8 groups).
Observations on adverse effects (brief): The inflammatory response was mild with electrospun PU and UPy-PC implants, inducing both more macrophages yet with relatively more type 2 macrophages present at an early stage than the PP mesh.
Timing of adverse effects: 60 to 180 days.
Factors that predict response: NR.

Source citation: Cheng et al. 2019[6]

Study Design: Comparative study
Device or Material: SMPU, PIII-SMPU, collagen coated SMPU, collagen coated PIII-SMPU
Route: Subcutaneous implant (in back)
Dose: 4 mm per implant
Frequency/ Duration: 4 implants per mouse (all 4 comparison implants)
Response: Inflammatory response.
Species (strain): IL-1β mice.
Gender: Male.
Number per group: 5 per group (1 group for each time point: 1, 3, 7, 14, 28 days).
Observations on adverse effects (brief): Results showed significantly lower acute/subacute inflammation in response to SMPU with PIII treatment + collagen coating compared to untreated SMPU, collagen coated untreated SMPU, and PIII treated SMPU, characterised by lower total cell numbers,

macrophages, neovascularisation, cellular proliferation, cytokine production, and matrix metalloproteinase production.
Timing of adverse effects: 1-28 days.
Factors that predict response: NR.

Source citation: Gerges et al. 2018[7]

Study Design: Comparative study
Device or Material: 4 different soft PU foam scaffolds
Route: Subcutaneous implant (in back)
Dose: 8 mm diameter, 4 mm height per implant
Frequency/ Duration: 4 implants per mouse (all 4 comparison implants)
Response: Foreign body response
Species (strain): Mice (CD1).
Gender: Female.
Number per group: 5 per group (1 group for each time point: 7, 28, 48, 91 days).
Observations on adverse effects (brief): No local gross adverse reactions were observed (redness, swelling, ulceration) in the skin overlying the scaffolds. All soft PU foam scaffolds elicited a foreign body response that was mainly characterized by infiltration of macrophages and multinucleated giant cells (MGCs), admixed with granulocytes and lesser numbers of lymphocytes and plasma cells. Evaluation of the inflammatory infiltrate revealed that the total inflammation and MGC scores increased over time for all scaffold types.
Timing of adverse effects: 7 to 91 days.
Factors that predict response: NR

Source citation: Heise et al. 2018[8]

Study Design: RCT
Device or Material: TPU mesh or PVDF mesh
Route: Abdominal wall implant
Dose: 200 x 100 mm
Frequency/ Duration: Single administration
Response: Foreign body reaction
Species (strain): Minipig.
Gender: Female.
Number per group: 5.
Observations on adverse effects (brief): CD68 did not show significant difference between TPU and PVDF (10.7 ± 1.9 vs. 8.9 ± 1.8, $p = 0.120$), while Ki67 positive cells were increased after abdominal wall replacement with TPU (17.9 ± 1.0 vs. 12.7 ± 3.5, $p = 0.003$). Evaluation of apoptosis indicated a higher number of apoptotic cells in the TPU group in comparison to PVDF (14.1 ± 3.6 vs. 9.3 ± 1.8, $p = 0.005$).
Timing of adverse effects: 8 weeks.
Factors that predict response: NR

Source citation: Huang et al. 2018[9]

Study Design: Comparative study
Device or Material: WBPU films vs PLA films
Route: Subcutaneous implant
Dose: 10 mm × 10 mm, 0.2 mm thickness

Frequency/ Duration: 2 films (1 of each type) per animal
Response: Foreign body reaction
Species (strain): Rat (Sprague-Dawley).
Gender: NR.
Number per group: 6.
Observations on adverse effects (brief): PU films assembled from PU NPs inhibit proinflammatory cytokines and macrophage polarization and present a smaller shifting foreign body reaction (FBR) in vivo than the conventional PLA.
Timing of adverse effects: 4 weeks.
Factors that predict response: NR.

Source citation: Lambertz et al. 2018[10]

Study Design: RCT
Device or Material: TPU vs PVDF mesh
Route: Abdominal wall implant
Dose: 10 × 20 cm
Frequency/ Duration: Single administration
Response: Foreign body reaction
Species (strain): Minipig.
Gender: Female.
Number per group: 5.
Observations on adverse effects (brief): Inner and outer foreign body granuloma sizes did not differ between the TPU and PVDF group (Inner granuloma: 6.1 ± 1.8 µm vs. 5.7 ± 1.6 µm, p = 0.101; Outer granuloma: 39.5 ± 13.7 µm vs. 41.4 ± 11.8 µm, p = 0.110). No fibrotic bridging between mesh filaments was observed in both groups. No significant differences in CD68, Ki67 and apoptotic cells between the study groups after 8 weeks. TPU meshes showed significant lower levels of CD45-positive cells in comparison to PVDF (2.4 ± 0.9 vs. 5.1 ± 2, p = 0.047).
Timing of adverse effects: 8 weeks.
Factors that predict response: NR.

Source citation: Liang et al. 2018[11]

Study Design: RCT
Device or Material: WBPU scaffolds with different pore sizes
Route: Subcutaneous implant
Dose: diameter 4.5 mm, thickness 2.0 mm
Frequency/ Duration: Single administration
Response: Inflammatory response.
Species (strain): SPF C57BL/6 mice
Gender: Female.
Number per group: (in 7 groups).
Observations on adverse effects (brief): On Day 3, 14, and 30, the serum levels of TNF-α and IL-10 revealed that the WBPU scaffolds did not promote inflammation in the mice and exhibited a somewhat anti-inflammatory characteristic The numbers of M1 macrophages in the scaffold groups were equal or lower than that in the control group, while the numbers of M2 macrophages were higher in each scaffold group on Day 3 and 14 than at the late stage of implantation (on Day 30).
Timing of adverse effects: 3 to 30 days.
Factors that predict response: NR.

Source citation: Sgrott et al. 2018[12]

Study Design: Comparative study
Device or Material: Polyester urethane sheets (Silimed) vs sham
Route: Dorsal subcutaneous implant
Dose: 2 cm wide x 2 cm long x 2 mm thick
Frequency/ Duration: Single administration
Response: Inflammatory response
Species (strain): Rat (Wistar).
Gender: Female.
Number per group: 7
Observations on adverse effects (brief): Plasma-heparin PCU grafts had higher patency rate at 2 weeks and 4 weeks compared to plasma-control (untreated) PCU grafts. At 2 weeks, approximately 71% (5 of 7) of plasma-control grafts remained patent, whereas 86% (6 of 7) of plasma-heparin grafts were patent. However, after 4 weeks, plasma-control grafts exhibited approximately 29% (2 of 7) patency, compared to 86% (6 of 7) patency of plasma-heparin grafts. Electrospun PCU grafts showed low immune responses and did not recruit large number of macrophages.
Timing of adverse effects: 2 to 4 weeks.
Factors that predict response: NR.

Source citation: Guo et al. 2017[13]

Study Design: Comparative study
Device or Material: PU scaffold vs VEGF-loaded PU scaffold
Route: Femoral artery graft implant
Dose: 5 cm x 3 mm implant
Frequency/ Duration: 2 scaffolds per dog (1 of each type
Response: Graft patency, Foreign body inflammation
Species (strain): Mongrel dogs.
Gender: Male.
Number per group: 8.
Observations on adverse effects (brief): At 6th month postoperatively, 5 of the 8 VEGF-loaded grafts were patent while all the 8 grafts without VEGF were occluded. Foreign-body inflammation with minimal chronic inflammation was found in the external of conduits.
Timing of adverse effects: 1 to 6 months
Factors that predict response: NR.

Source citation: Qiu et al. 2017[14]

Study Design: Comparative study
Device or Material: PCU graft vs heparin-PCU graft
Route: Carotid artery implant
Dose: 1 mm diameter, 1 cm length
Frequency/ Duration: Single administration
Response: Graft patency, Inflammatory response
Species (strain): Rat (Sprague Dawley).
Gender: Male.
Number per group: 7.
Observations on adverse effects (brief): Plasma-heparin PCU grafts had higher patency rate at 2 weeks and 4 weeks compared to plasma-control (untreated) PCU grafts. At 2 weeks, approximately 71% (5 of 7) of plasma-control grafts remained patent, whereas 86% (6 of 7) of plasma-heparin grafts were patent. However, after 4 weeks, plasma-control grafts exhibited approximately 29% (2 of 7) patency, compared to 86% (6 of 7) patency of plasma-heparin grafts. Electrospun PCU grafts showed low immune responses and did not recruit large number of macrophages.
Timing of adverse effects: 2 to 4 weeks.
Factors that predict response: NR.

Source citation: Lambertz et al. 2016[15]

Study Design: RCT
Device or Material: TPU, PP mesh
Route: Abdomen
Dose: 3 x 3 cm2
Frequency/ Duration: Single administration/ 7 and 21 days
Response: Adhesions, Foreign body granulomas
Species (strain): Rabbit (New Zealand White).
Gender: Female.
Number per group: 8.
Observations on adverse effects (brief): Significantly more adhesions (at both follow-ups), and smaller outer granuloma sizes (at 21 days) with PP. No significant differences were reported in immunohistochemical observations (inflammatory cells (CD68), proliferating cells (Ki67), and apoptotic cells), or collagen type I/III ratio. Elastic properties of TPU mesh remained at 7 and 21 days.
Timing of adverse effects: NR.
Factors that predict response: NR.

Source citation: Roman et al. 2016[16]

Study Design: Comparative study
Device or Material: PU, PP, PLA, PVDF mesh
Route: 2 upper quadrants of the abdominal wall parallel to the midline
Dose: Two 20 x 5 mm defects
Frequency/ Duration: Single administration
Response: Adhesions, Fibrosis, Inflammation, Mesh exposure
Species (strain): Rabbits (New Zealand).
Gender: Male.
Number per group: 40; 8 each polypropylene (PP), polyurethane (PU), polyvinylidene fluoride (PVDF), poly-L-lactic acid (PLA), and sham.
Observations on adverse effects (brief): PPL and PVDF meshes demonstrated a sustained chronic inflammatory response profile (M1 response) vs PLA and PU groups (M2 response). Excessive fibrotic tissue formation by 90 days was noted in PPL and PVDF arms. Complications: 5 mesh exposure at 30 days (3 PPL, 2 PVDF), 6 adhesions at day 30 (1 PPL, 3 PU, 2 sham), 6 adhesions at day 90 (1 PPL, 5 PLA).
Timing of adverse effects: 30 and 90 days.
Factors that predict response: NR.

Source citation: Silva et al. 2016[17]

Study Design: Comparative study
Device or Material: PU nanoparticles vs saline control
Route: Oral gavage or intraperitoneal injection
Dose: 2 mg/kg, 5 mg/kg or 10 mg/kg
Frequency/ Duration: Single administration
Response: Inflammatory response
Species (strain): Swiss albino mice.
Gender: Male.
Number per group: 6 (8 different groups based on dose and route of administration).
Observations on adverse effects (brief): No toxicity observed. However, inflammatory infiltration in the lung was identified in mice treated by i.p. route, for all nanoparticle concentrations evaluated. The obtained frequencies are 3 mice with lung inflammation in 6 analyzed mice (i.e. 3/6) treated with 5

mg/kg/day and 4/6 mice treated with 10 mg/kg/day. Liver treated by i.p. with 2, 5 and 10 mg/kg/day showed vascular congestion and vacuolization of hepatocytes (6/6, 5/6 and 6/6, respectively). Kidney of mice treated with 5 and 10 mg/kg/day by the same route also showed glomerular necrosis (3/6 in both treatment). Orally treated mice revealed vascular congestion and vacuolization of hepatocytes, better visualized in the figures corresponding to the liver of mice treated with 2 and 10 mg/kg/day (5/6 in both treatment), as well as inflammatory infiltrate in the liver of mice treated with 5 mg/kg/day (6/6). Lung of orally treated mice with 5 and 10 mg/kg/day showed inflammation (4/6, respectively), and kidney treated with the same doses showed glomerular necrosis (5/6 in both treatment). Lung evaluation also revealed inflammatory infiltrate after treatment with all PU-NPs concentrations evaluated and glomerular atrophy in the kidney of mice treated with 5 and 10 mg/kg/day.

Timing of adverse effects: 10 days.
Factors that predict response: NR.

Source citation: Wang et al. 2016[18]

Study Design: Comparative study
Device or Material: TPU nanofiber membrane vs TPU microfiber membrane
Route: Abdominal implant
Dose: NR
Frequency/ Duration: 2 implants per animal
Response: Foreign body reaction
Species (strain): Rats (Sprague Dawley), C57BL/6 mice.
Gender: Male.
Number per group: NR.
Observations on adverse effects (brief): TPU-nano caused minimal macrophage responses and induced only mild foreign body reactions compared to TPU-micro membranes.
Timing of adverse effects: 2 months
Factors that predict response: NR.

Source citation: Lambertz et al. 2015[19]

Study Design: RCT
Device or Material: TPU thread (Chronoflex C93A), PP thread (Prolene)
Route: Abdominal suturing
Dose: 15 cm suture
Frequency/ Duration: Single administration
Response: Immune response
Species (strain): Rabbit (Chinchilla).
Gender: Female.
Number per group: 10.
Observations on adverse effects (brief): the TPU suture showed significantly less CD68 positive cells ($p < 0.001$) and a higher collagen I/III ratio (p 5 0.011) than PP did after 21 days. The amount of apoptotic cells was significantly elevated in the TPU group (p 5 0.007) after 21 days. No differences were found concerning granuloma size and number of Ki67- positive cells.
Timing of adverse effects: 7 and 21 days.
Factors that predict response: NR.

Source citation: Pontailler et al. 2015[20]

Study Design: Comparative study
Device or Material: PU, PDO, and PHBVV patches

Route: Inferior vena cava implant
Dose: NR
Frequency/ Duration: Single administration
Response: Granuloma
Species (strain): Rat (Wistar).
Gender: Female.
Number per group: PDO 18, PU 21, or PHBVV 14.
Observations on adverse effects (brief): No stenosis, thrombosis, or aneurysm in the area of the patch implantation in any group. In the PU group, granulomas were found in 4 (22%) of the 18 patches at 6 weeks and in all specimens at 3 months
Timing of adverse effects: 6 weeks to 3 months.
Factors that predict response: NR.

Source citation: Vogels et al. 201521

Study Design: Comparative study
Device or Material: medical-grade TPU sutures from three different suppliers (DSM N.V., Heerlen, Netherlands; AdvanSource Biomaterials Corp., Wilmington, MA; and Lubrizol Corp., Wickliffe, OH) vs PP sutures (control)
Route: abdominal subcutaneous tissue implant
Dose: 3 cm threads of each material per animal
Frequency/ Duration: Experimental and control threads placed in each animal, tissue samples collected at 7 and 21 days
Response: Foreign body response
Species (strain): Wistar rats.
Gender: Male.
Number per group: 48.
Observations on adverse effects (brief): The new TPU sutures showed an improved foreign body response when compared with that of PP, with a reduction in the amount of macrophages surrounding the material. No differences were found concerning granuloma size.
Timing of adverse effects: 7 and 21 days.
Factors that predict response: NR.

Source citation: Wu et al. 2015[22]

Study Design: RCT
Device or Material: PU degradation products vs saline control
Route: Tail vein injection
Dose: PU 0.1 g/mL, injections 5 mL/kg/day
Frequency/ Duration: Single administration/ day at 7 to 16 days gestation
Response: Maternal and developmental toxicity (none observed)
Species (strain): Rat (Sprague Dawley).
Gender: Pregnant females.
Number per group: 21 (PU groups), 11 (saline control groups).
Observations on adverse effects (brief): No maternal toxicity was observed. No external, skeletal, and visceral malformations in fetuses were found associated with the test materials, implying their safety to both adult rats and the offspring
Timing of adverse effects: 20 days.
Factors that predict response: NR.

Source citation: Rodriguez et al. 2014[23]

Study Design: Case series

Device or Material: Filling devices fabricated out of polyurethane SMP foams
Route: Implant in aneurysm
Dose: Implant 8 to 12 mm in diameter, 2 per animal
Frequency/ Duration: 2 implants per animal, 1 in each aneurysm
Response: Inflammatory response
Species (strain): Swine.
Gender: NR
Number per group: Mild inflammation at 30 days, minimal inflammation at 90 days
Observations on adverse effects (brief):
Timing of adverse effects: 30 to 90 days.
Factors that predict response: NR.

Source citation: Cunningham et al. 2013[24]

Study Design: RCT
Device or Material: 1) sham (control); 2) stainless steel 316LVM; 3) titanium alloy Ti-6AL-4 V; 4) cobalt chromium alloy; 5) UHMWPe; 6) ZTA ceramic; 7) PTFE; 8) PCU; 9) silicone; 10) PET; 11) polyester; and 12) PEEK.
Route: Lumbar spinal implant
Dose: 1E+08/mg to 2E+10/mg of particulate material per animal
Frequency/ Duration: Single implant
Response: Local inflammatory response in epidural fibrous tissue
Species (strain): Harlan Sprague-Dawley New Zealand White rabbits.
Gender: NR.
Number per group: 10.
Observations on adverse effects (brief): All experimental animals, particularly those in which metallic materials (stainless steel, cobalt chrome, or titanium alloy) were used, exhibited markedly greater amounts of epidural fibrosis compared with the operative sham treatment and polymeric treatment groups. The polymeric and ceramic treatment groups (PTFE, PCU, silicone, PET, polyester, PEEK, and ZTA ceramic) as a whole produced less reactivity in macrophages and cytokine response at both the 3- and 6-month postoperative intervals than the corresponding metallic treatment groups. No significant pathological changes induced by any of the 11 experimental treatments or sham procedure.
Timing of adverse effects: 3 to 6 months.
Factors that predict response: NR.

Source citation: Bergmeister et al. 2012[25]

Study Design: Case series
Device or Material: PU vascular grafts
Route: Vascular graft implant
Dose: Length: 15 mm; inner diameter: 1.5 mm
Frequency/ Duration: Single administration
Response: Graft patency, Foreign body reaction (none)
Species (strain): Rat (Sprague Dawley).
Gender: Male.
Number per group: 10 (4 groups, 1 group per timepoint at 7 days, 1 month, 3 months, and 6 months.
Observations on adverse effects (brief): no evidence of foreign body reaction or graft degradation. The overall patency rate of the intravascular implants was 95%.
Timing of adverse effects: 1 week to 6 months.
Factors that predict response: NR.

Source citation: Hu et al. 201226

Study Design: RCT
Device or Material: PU or PTFE vascular grafts
Route: Vascular graft implant
Dose: Inner diameter of 4 mm
Frequency/ Duration: Single administration
Response: Graft patency, Rupture
Species (strain): Dog (beagle).
Gender: Male.
Number per group: 24 (6 for each of 4 time points).
Observations on adverse effects (brief): Four weeks after the surgery, one dog with a PU graft died due to rupture at the anastomotic site. The graft patency rate was significantly higher in the group with PU grafts compared with the group with PTFE grafts ($p = 0.02$). At 24 weeks, some anastomotic sites of PTFE grafts became stenotic ($p = 0.013$ vs. PU group).
Timing of adverse effects: 4 to 24 weeks.
Factors that predict response: NR.

Source citation: Zhou et al. 2011[27]

Study Design: Comparative study
Device or Material: pH-sensitive PU films
Route: Intramuscular implant
Dose: NR
Frequency/ Duration: Single administration
Response: Inflammatory response (none observed).
Species (strain): Rat (Sprague Dawley).
Gender: Male and Female.
Number per group: 3 (5 groups based on timepoint).
Observations on adverse effects (brief): the pH-sensitive PU films were easily degraded in vivo and the degradation products did not induce any adverse response from surrounding muscle tissues.
Timing of adverse effects: 1 to 12 weeks.
Factors that predict response: NR.

Source citation: Bezuidenhout et al. 2010[28]

Study Design: Comparative study
Device or Material: PU disk vs heparinized PU disk
Route: Subcutaneous implant
Dose: 2 mm disk thickness
Frequency/ Duration: 2 disks/rat (1 of each type)
Response: Inflammatory response
Species (strain): Rat (strain NR).
Gender: NR.
Number per group: 8 rats total, each received 1 disk of each type.
Observations on adverse effects (brief): No significant difference could be detected between the inflammatory response, as quantified by the areas occupied by these two cell types, elicited by the two disk types (PU control: 5.9 ± 0.8 vs. Heparinized: $4.9 \pm 0.5\%$; $p = 0.36$).
Timing of adverse effects: 28 days.
Factors that predict response: NR.

Source citation: Xie et al. 2010[29]

Study Design: RCT
Device or Material: PEU (Pulse-Tec), PCU-PET (Corvita), PEUU-PET (Thoratec-NR, SR, DR) vascular grafts
Route: Vascular graft implant
Dose: Implant 6 mm in diameter
Frequency/ Duration: Single administration
Response: Graft patency, Graft degradation
Species (strain): Mongrel dogs.
Gender: NR.
Number per group: 2 (5 groups).
Observations on adverse effects (brief): All grafts were patent. Three types of PEUU-PET graft exhibited a high degree of thrombus and little tissue in-growth, and were non-adhesive to both the inner and external capsules as the solid layer beneath their lumens completely blocked any transmural communication. The microporous PEUU degraded extensively. PEU grafts at one month also demonstrated non-adhesive properties because the external skin served as a barrier to tissue in-growth. At 6 months, its PEU wall displayed the most severe degradation, damaging graft structural integrity and causing significant tissue deposition in the degradation areas
Timing of adverse effects: 1 to 6 months.
Factors that predict response: NR.

dPCU: degradeable thermoplastic polycarbonate urethane; ePTFE: expanded polytetrafluoroethylene; NA: not applicable; NR: not reported; PLA: poly-L-lactic acid; PP: polypropylene; PU: polyurethane; PVDF: polyvinylidene fluoride; RCT: randomized controlled trial; SMPU: shape memory polyurethane; TPU: thermoplastic polyurethane; UPy-PC: ureidopyrimidinone-polycarbonate. WBPU: waterborne polyurethane.

Table 10: Intravascular Catheters – Health Effect (In Vivo) Human Studies

Source citation: Fabiani et al. 2020[30]

Study Design: Retrospective controlled cohort
Device Material: Power injectable PUR MCs vs. polyethylene LPCs
Contact Duration: 153 days for MCs, 48 to 54 days for LPCs
Dose: MCs: 4-5 Fr, 20 cm; LPCs: 3 Fr, 8 cm; 4 Fr, 10 cm; 4 Fr, 18 cm
Frequency/ Duration: 1 attempt: 91.3%; 2 attempts: 8.2%; 3 attempts: 0.5%
Response: Catheter Fissuration, Complete catheter occlusion, CRT, Drug leakage
Patient characteristics (gender, mean age): 53% males, 70 years.
Number per group: 80 MC, 48 LPC at 18 cm, 56 LPC at 8/10 cm.
Observed adverse effects: Complications with MCs included 4 (30.8%) symptomatic CRT, 3 (23.1%) each for complete catheter occlusion and drug leakage from the exit-site, and 2 (15.4%) catheter fissuration. Symptomatic CRT was higher with MCs vs. LPCs (30.8% MC, 12.5% and 10% for LPCs).
Timing of adverse effects: NR.
Factors that predict response: NR.

Source citation: Lv and Zhang 2020[31]

Study Design: Systematic review
Device Material: PUR catheter (Vialon) vs. a PTFE catheter (Teflon)
Contact Duration: Overall catheter use (days): range 1.5±2.7 to 12±8.6
Dose: NR
Frequency/ Duration: NR
Response: Phlebitis
Patient characteristics (gender, mean age): 53.9% male, 57.1 years.
Number per group: 35 studies included; 20,697 catheters in 15,791 patients.

Observed adverse effects: Incidence of phlebitis was lower with Vialon vs. Teflon (26.5% (95% CI: 21 to 32%) Vialon, 33% (95% CI: 25 to 41%) Teflon).
Timing of adverse effects: 1.5 to 21 days.
Factors that predict response: Female gender and use of Teflon catheter were risk factors for phlebitis.

Source citation: Mariggio et al. 2020[32]

Study Design: Prospective controlled cohort
Device Material: PUR PICC (Power) vs. silicone PICC (Groshong); both Bard Access Systems
Contact Duration: Median dwell (days): 94 (IQR 44-152)
Dose: Bi-lumen 5 Fr PUR; single lumen, 4 Fr Groshong
Frequency/ Duration: NR
Response: CRT, Malfunction, Malposition, Obstruction , Rupture
Patient characteristics (gender, mean age): 62% male, 51.5 years.
Number per group: 52 PUR, 48 silicone; allo-HSCT recipients.
Observed adverse effects: 5 (9.6%) CRT with PUR; higher incidence vs. silicone (8.3%). Mechanical complications (overall 8 malfunctions, 4 obstructions, 2 ruptures, 1 malposition) occurred in 9 (17.3%) individuals with PUR, and 6 (12.5%) with silicone.
Timing of adverse effects: Median time to a thrombotic event was 37 days (IQR 10-45). Mechanical complications occurred after day 100 in 6 (40%).
Factors that predict response: NR.

Source citation: Takahashi et al. 2020[33]

Study Design: Controlled cohort
Device Material: PUR PIVC (Surflo V3; Terumo Corporation); vs. PTFE catheter (Teflon)
Contact Duration: NR
Dose: NR
Frequency/ Duration: 1 attempt: 49.4%, ≥2 attempts: 50.6%
Response: Mechanical failure composite (complete dislodgement, occlusion, phlebitis, infection)
Patient characteristics (gender, mean age): 61.8% male, 66.9 years.
Number per group: PUR: 160 (189 catheters); PTFE: 157 (233 catheters).
Observed adverse effects: Higher mechanical failure with PTFE (29.2% vs. 21%). Catheter failure per 1,000 catheter days was 35.0/1,000 catheter days with PUR vs. 89.5/1,000 days with PTFE. Relative risk reduction of catheter failure with PUR was >60% (95% CI: 0.47 to 0.71; NNT 6.04).
Timing of adverse effects: NR.
Factors that predict response: softness of PUR catheter.

Source citation: Trezza et al. 2020[34]

Study Design: Cohort
Device Material: PUR PICC
Contact Duration: 4 months
Dose: 4 Fr
Frequency/ Duration: 1 attempt
Response: CRT, Fibroblastic sleeve
Patient characteristics (gender, mean age): NR
Number per group: PUR: 254 oncological/hematological patients (254 PICCs).
Observed adverse effects: CRT occurred in 14 (5.51%) patients: asymptomatic CRT in 13 (5.12%) patients; symptomatic CRT in 1 (0.39%) leukemia patient. Fibroblastic sleeve was detected in 76 (29.9%) patients; all asymptomatic and not associated with catheter malfunction. Authors noted an association of fibroblastic sleeve and CRT in 2 (0.78%) cases.
Timing of adverse effects: CRT: 8 cases by day 7, 6 cases day 7-14. Fibroblastic sleeve: 45 (17.7%) on day 7, 26 (10.2%) on day 14, 3 (1.2%) on day 21, 2 (0.79%) on day 28.
Factors that predict response: NR.

Source citation: Gnannt et al. 2019[35]

Study Design: Retrospective controlled cohort
Device Material: PUR PICC vs. Silicone
Contact Duration: Mean dwell (days): 112 (range 1 – 429)
Dose: Before venogram: 4.1 Fr, number of lumens: 1.47
Frequency/ Duration: NR
Response: Malposition, Obstruction, Thrombosis
Patient characteristics (gender, mean age): 59% female, 2.7 years.
Number per group: 46 PUR, 54 silicone with abnormal contrast venogram during upper extremity PICC. CVS/O with connection (Group A) vs. without connection (Group B) to superior vena cava (SVC). Group B: Absence of visible connection to SVC.
Observed adverse effects: Before venogram, Group B was associated with significantly higher usage of PUR catheters as a prior CVAD (70% vs. 25%) and greater incidence of malposition (30% vs. 13%) (p=0.002). After venogram, significantly more thrombosis was diagnosed in Group B (36% vs. 8%; p=0.002).
Timing of adverse effects: NR.
Factors that predict response: NR.

Source citation: LaRusso et al. 2019[36]

Study Design: Retrospective controlled cohort
Device Material: Non-tunneled PUR PICC vs. tunneled silicon PICC vs. tunneled silicone Broviacs catheter
Contact Duration: PICC access/patient: 342 days (range 35 days to 8 years)
Dose: PICCs: 1.2-4 Fr; Broviacs: 2.7-7 Fr
Frequency/ Duration: NR
Response: Breakage, Dislodgement, Migration or retraction, Occlusion, Stenosis
Patient characteristics (gender, mean age): 51% female; 57 days PICC, 122 days Broviacs
Number per group: 37 patients with intestinal failure. 209 PICCs (85% PUR, 15% silicone), 39 tunneled silicone Broviacs.
Observed adverse effects: PUR PICCs had significantly higher rates of occlusion vs. Broviacs (Rate Ratio (RR) 3.35, 95% CI: 1.65 to 6.75; p<0.001), significantly lower rates of breakage (RR 0.22, 95% CI: 0.07 to 0.62; p=0.006), higher dislodgement rates (RR 3.37, 95% CI: 0.86 to 18.30; p=0.112), and higher stenosis rates (RR 4.45, 95% CI: 1.08 to 24.50; p=0.056). Rate of migration or retraction was 1.90 per 1,000 catheter days for PICC (vs. 0.15 for Broviacs). Authors noted the rate of silicone breakage was 6.4 times greater than PUR catheters per line/per catheter day (95% CI: 2.48 to 18.8; p=0.0003).
Timing of adverse effects: NR.
Factors that predict response: NR.

Source citation: Lopes et al. 2019[37]

Study Design: RCT
Device Material: PUR non-tunneled CVC with/without ELT
Contact Duration: Insertion days to first event (mean±SD): 9.9±4.9 ELT, 11.9±5.1 controls
Dose: PICCs: Double-lumen
Frequency/ Duration: NR
Response: Breakage, Obstruction
Patient characteristics (gender, mean age): ELT: 54% female, 40.4 days; Controls: 46% female, 43 days.
Number per group: 35 ELT, 39 controls.
Observed adverse effects: Catheter obstruction and catheter breakage occurred in 1 and 10 patient(s), respectively (all ELT).
Timing of adverse effects: mean 9.9 days.
Factors that predict response: Use of ethanol on the catheter. Use of "old-fashioned" PUR catheters.

Source citation: Picardi et al. 2019[38]

Study Design: RCT
Device Material: Open-ended, nonvalved, pressure injectable PUR PICC (EU-25541-HP Arrow, Teleflex Medical) vs. external, non-tunneled heparin-coated Vialon CVC (Becton-Dickinson)
Contact Duration: Median followup (days): 30 (range, 7-30)
Dose: PICC: 63% 5 Fr, 30% 4 Fr, 63% double lumen, 30% single lumen; CICC: 74% 7 Fr, 25% 8 Fr, 57% triple lumen, 42% double lumen
Frequency/ Duration: Median attempts: 1 (range 1-3)
Response: CRT, Dislocation, Occlusions, Rupture
Patient characteristics (gender, mean age): 50% male, 53.8 years.
Number per group: 46 PICC, 47 CICC.
Observed adverse effects: CRT significantly lower with PICC (8.7% vs. 25%; p=0.03); incidence rate 2.9/1,000 catheters per day for PICC. Catheter malfunctions (2 occlusions, 1 dislocation, 1 rupture) lower with PICC (8.6% vs. 10.6%).
Timing of adverse effects: CRT: median 10 days (range, 7-10 days).
Factors that predict response: NR.

Source citation: Seckold et al. 2019[39]

Study Design: Retrospective cohort
Device Material: PUR PICC vs. silicone PICC
Contact Duration: Mean days in situ: 33.4±36.1 PICC
Dose: Single lumen: 42% PUR, 69% silicone; dual lumen: 58% PUR, 33% silicone
Frequency/ Duration: M 1 attempt: 84%; 2-4 attempts: 16%
Response: Migration, Occlusion, Thrombus
Patient characteristics (gender, mean age): 57% male, 56.5 years.
Number per group: 154 PUR, 141 silicone.
Observed adverse effects: Complications with PUR included 9 (5.8%) migration, 5 (3.2%) occlusion, and 4 (2.6%) thrombus.
Timing of adverse effects: Bulk removal of PICC 5 to 15 days.
Factors that predict response: NR.

Source citation: Kleidon et al. 201840

Study Design: RCT
Device Material: PUR PICCs (Cook™ power-injectable (Cook Medical) vs. BioFlo (AngioDynamics))
Contact Duration: Median (IQR) dwell (days): 12.9 (9-14.1) Cook, 13.8 (10-17.3) BioFlo
Dose: 3 Fr: 77% Cook, 81% BioFlo; 4 Fr: 23% Cook, 19 BioFlo
Frequency/ Duration: 1 attempt: 81% Cook, 90% BioFlo; ≥2 attempts: 19% Cook, 10% BioFlo
Response: Breakage, Dislodgement, Occlusion, Thrombosis
Patient characteristics (gender, mean age): PUR: 55% male, 7.5 years
Number per group: 75 each arm.
Observed adverse effects: Complications with Cook PICC included 11 (15%) partial occlusion, 10 (14%) complete occlusion, 6 (8%) thrombosis, 3 (4%) CVAD breakage, 2 (3%) partial dislodgement. Complications with BioFlo included 5 (7%) partial occlusion, 2 (3%) complete occlusion, 2 (3%) thrombosis, and 2 (3%) complete dislodgement.
Timing of adverse effects: median days to first complication: 4.
Factors that predict response: NR

Source citation: Poletti et al. 2018[41]

Study Design: Retrospective cohort
Device Material: PUR PICC (including power injectable triple-lumen 6 F, and single-lumen 3F (Medcomp Co.) and double-lumen 4F (AlfaMed))

Contact Duration: Mean dwell (days): 13±3.5
Dose: 3 lumens 6 Fr (39.4%), 2 lumens 4 and 5 Fr (57.6%), 1 lumen 3 and 5 Fr (3%)
Frequency/ Duration: 1 attempt
Response: Thrombosis
Patient characteristics (gender, mean age): 58.4% male, 72.7 years.
Number per group: 137 PICCs.
Observed adverse effects: Catheter-related peripheral venous thrombosis occurred in 19 (13.8%) patients; symptomatic in 2 (1.45%) patients, asymptomatic in 17 (12.4%) patients
Timing of adverse effects: vascular ultrasound: 7 days post-placement and at removal.
Factors that predict response: NR

Source citation: Xu et al. 2018[42]

Study Design: Retrospective controlled cohort
Device Material: PUR PICC with no valve (Medcomp Co.) vs. silicone PICC with valved tip (Groshong, Bard)
Contact Duration: Mean dwell (days): 165.9 PUR, 176.6 silicone
Dose: Single lumen, 4F
Frequency/ Duration: NR
Response: CRT, Dislodgement, Obstruction
Patient characteristics (gender, mean age): PUR: 81% male, 57.3 years. Groshong: 70% male, 56 years.
Number per group: 80 PUR, 78 silicone.
Observed adverse effects: Complications included 5 obstructions, 2 CRT, and 6 dislodgements. Incidence rates per 1,000 catheter days were 0.15 for CRT, and 0.45 for dislodgement. Incidence rates per 100 patients for obstruction was 6.25.
Timing of adverse effects: NR.
Factors that predict response: NR.

Source citation: Gnannt et al. 2017[43]

Study Design: Retrospective controlled cohort
Device Material: PUR PICC vs. silicone PICC (manufacturers included Cook, Medcomp, Bard Medical)
Contact Duration: Mean time until breakage (days): 57.9 days
Dose: Breakage: 206 single-lumen, 29 double-lumen; mostly 3 F
Frequency/ Duration: 72% of 161 were 1 attempts
Response: Breakage
Patient characteristics (gender, mean age): 3 years and 4 months.
Number per group: 3967 silicone and PUR PICCs.
Observed adverse effects: Of the 235 first-time PICC breaks, 66 were PUR (19 were 4 Fr double-lumen), and 169 were silicone
Timing of adverse effects: Breakage occurred from 30 days to 560 days.
Factors that predict response: NR.

Source citation: Gnannt et al. 2016[44]

Study Design: Retrospective controlled cohort
Device Material: PUR PICC vs. silicone PICC
Contact Duration: NR
Dose: Overall 74% were 3 Fr, 17% were 4 Fr
Frequency/ Duration: NR
Response: PICC movement
Patient characteristics (gender, mean age): 63% male, 31 months.
Number per group: 80 PUR, 32 silicone.
Observed adverse effects: PUR PICCs moved significantly more than silicone PICCs. Arm movement from positions 1 to 2: mean range of tip movement (rib units) was 0.5 for PUR and 0.3 for silicon. Arm movement from positions 2 to 3, mean range of motion (rib units) was 0.5 for PUR and 0.1 for silicone ($p<0.05$). Arm movement from positions 1 to 3, the mean range of motion (rib units) was

1.0 for PUR, and 0.4 for silicone ($p<0.05$). Multivariate regression analysis of all 3-Fr single-lumen PICCs indicated that PUR PICCs moved a mean of 0.61 rib spaces more than silicone PICCs ($p<0.0001$).

Timing of adverse effects: NR
Factors that predict response: NR

Source citation: Tanabe et al. 2016[45]

Study Design: Retrospective controlled cohort
Device Material: PUR PIVC (Surflo® V3; Terumo Corp.) vs. Teflon PIVC (Surshield® and Surflo 2; Terumo)
Contact Duration: Median (hours): 50 PUR
Dose: 22 gauge: >80%; 24 gauge: 18%
Frequency/ Duration:
Response: Erythema, Pain, Phlebitis, Swelling
Patient characteristics (gender, mean age): PUR: 65% male, 68 years. Teflon: 58% male, 70 years.
Number per group: 207 PUR (153 patients), 200 Teflon (154 patients).
Observed adverse effects: Complications included phlebitis (17% PUR vs. 37% Teflon; $p<0.001$), erythema (13.5% PUR vs. 31% Teflon; $p<0.001$), swelling (26.6% PUR, 25.5% Teflon), palpable venous cord (7.2% PUR, 8.5% Teflon), and pain (10.6% PUR, 21% Teflon; $p=0.006$).
Timing of adverse effects: median 50 hours.
Factors that predict response: NR

Source citation: Ulloa-Ricardez et al. 2016[46]

Study Design: Case control
Device Material: PUR CVC (Arrow) vs. silicone CVC (Bioflux); EB-PICC percutaneous (material NR)
Contact Duration: NR
Dose: Thrombosis occurred mostly with 4 Fr, 2 lumen
Frequency/ Duration: NR
Response: Intracardiac thrombosis
Patient characteristics (gender, mean age): Cases: 51% males, 32.4 weeks.
Number per group: 43 neonates each with/without intracardiac thrombosis in the RA or SVC.
Observed adverse effects: Intracardiac thrombosis occurred in 37/43 (86%) neonates using PUR CVC.
Timing of adverse effects: NR
Factors that predict response: Maternal history of gestational diabetes/DM was associated with thrombosis in the RA or SVC of neonates.

Source citation: Dupont et al. 2015[47]

Study Design: Prospective cohort
Device Material: PUR PICC (TurboJect®; Cook)
Contact Duration: Dwell (days): 15±9
Dose: Single lumen 4 Fr (103), 5 Fr (71)
Frequency/ Duration: 1 attempt (76), 2 attempts (24), ≥3 attempts (13)
Response: Displacement, Obstruction, Persistent pain, Thrombosis
Patient characteristics (gender, mean age): 65% female, 45.5 years.
Number per group: 174 PICCs (117 patients).
Observed adverse effects: Complications included 4 (2%) symptomatic upper limb DVT and 4 (2%) symptomatic superficial upper limb vein thrombosis, 1 spontaneous catheter tip displacement in the jugular vein, 18% catheter obstruction, and 18% persistent pain after insertion.
Timing of adverse effects: 1 to 96 days dwell time.
Factors that predict response: NR

Source citation: Fabiani et al. 2015[48]

Study Design: Prospective cohort
Device Material: PUR CVC (Arrow MAC Si-11142; Teleflex Medical)
Contact Duration: Mean dwell (days): 3.9±2
Dose: 10 cm, 7-8 Fr, double lumen
Frequency/ Duration: NR
Response: CRT, Fibrin sleeve
Patient characteristics (gender, mean age): 75% males, 69.1 years.
Number per group: 116
Observed adverse effects: Incidence of thrombotic events (CRT and fibrin sleeve not associated with thrombosis) was 51.7%. CRT occurred in 31 (26.7%) patients; 70.5 cases per 1,000 catheter days. Fibrin sleeves were detected in 33 (28.4%) patients.
Timing of adverse effects: US followup for CVCs were performed 24 and 48 hours after CVC placement and 24 hours after removal; dwell times ranged from 1 to 12 days.
Factors that predict response: Female gender had a significantly higher risk of CRT.

Source citation: Seckold et al. 2015[49]

Study Design: Systematic review
Device Material: PUR PICCs (power injectable Bard Power PICC Solo2, Cook Turbo-ject, Vaxcel, Olimpicc, LIFECATH) vs silicone (Bard Groshong)
Contact Duration: NR.
Dose: 4 to 6 Fr, single and double lumen
Frequency/ Duration: NR.
Response: Dislodgement, Kinking, Migration, Occlusion, Pain, Phlebitis, Rupture, Thrombosis
Patient characteristics (gender, mean age): NR
Number per group: Enrollments ranged from 50 to 500 in 9 studies examining PUR
Observed adverse effects: Overall, higher rates of phlebitis (15% vs. 8.3%) and occlusion (9% vs. 8%) occurred with PUR. Complications from PUR PICCs included thrombosis (range 0.7% to 5.23%), phlebitis (range 2.6% to 70%), occlusions (range 0.9% to 20%), dislodgement (range 3.1% to 6%), kinking (5.26%), rupture (0.5%), migration (1%), and pain (2.63%).
Timing of adverse effects: NR
Factors that predict response: NR.

Source citation: Can et al. 2014[50]

Study Design: Cohort
Device Material: PUR PICCs (Nutriline and PremiCath; Vygon Corp)
Contact Duration: 11.58 days non-central, 12.53 days central
Dose: 1 Fr
Frequency/ Duration: 1 attempt (85%), 2 attempts (15%)
Response: Dislodgement, Local edema, Occlusions, Redness/swelling
Patient characteristics (gender, mean age): 59.3% males, 28 weeks.
Number per group: 123 (135 PICCs).
Observed adverse effects: 28 (22.7%) occlusions, 6 (4.8%) dislodgements, 23 (18.6%) redness or swelling, and 12 (9.7%) local edema.
Timing of adverse effects: NR.
Factors that predict response: NR.

Source citation: Costa et al. 2014[51]

Study Design: Prospective cohort
Device Material: PUR PICC (Nutriline Twinflo; Vygon) vs. silicone (BD First PICC; Becton, Dickinson)

Contact Duration: 13.9±9.1 days PUR
Dose: Dual-lumen 2.0 Fr PUR; single-lumen 1.9 Fr silicone
Frequency/ Duration: NR.
Response: Dislodgement, Extremity edema, Leakage, Migration, Occlusion, Rupture
Patient characteristics (gender, mean age): PUR: 61.5% males, 10.6 days.
Number per group: 91 PUR, 156 silicone (191 neonates).
Observed adverse effects: omplications (based on 44 individuals with non-elective removal) included 5 (11.4%) occlusion, 4 (9.1%) rupture, 7 (15.9%) dislodgement, 5 (11.4%) migration, 6 (13.6%) extremity edema, and 2 (13.6%) leakage.
Timing of adverse effects: NR.
Factors that predict response: NR.

Source citation: Pittiruti et al. 2014[52]

Study Design: RCT
Device Material: 3 power-injectable PUR PICCs: Power PICC Solo (Bard) vs. Xcela PICC with proximal valve 'PASV' (Navilyst) vs. ProPICC with no valve (Medcomp)
Contact Duration: Mean dwell (days): 56±23 Solo, 64±31 PASV, 65±27 no valve
Dose: Single lumen, 4 Fr
Frequency/ Duration: NR.
Response: Occlusions, Ruptures, Thrombosis
Patient characteristics (gender, mean age): Solo: 36% male, 64 years. PASV: 38% male, 61 years. No valve: 33% male, 62 years.
Number per group: 61 Solo, 60 PASV, 59 no valve.
Observed adverse effects: 6 occlusions (3 Solo, 1 PASV, 2 no valve), 5 thrombosis (1 symptomatic thrombosis with PASV, 2 asymptomatic with Solo, 1 asymptomatic each with PASV and no valve), and 3 intravascular ruptures with Solo (potentially defective batch).
Timing of adverse effects: NR.
Factors that predict response: NR.

Source citation: Gentile et al. 2013[53]

Study Design: Prospective cohort
Device Material: Aromatic SCVC (Blue FlexTip®; Arrow International) vs. aliphatic SCVC (Seldiflex®; Prodimed-Plastimed)
Contact Duration: Median days: 13 (IQR: 8 to 19)
Dose: Mostly 3 lumen, 7 Fr
Frequency/ Duration: NR.
Response: Occlusion, SCVC-related DVT
Patient characteristics (gender, mean age): 81% male, 38±16 years.
Number per group: 84 Ar SCVC, 102 AI SCVC.
Observed adverse effects: Total SCVC-related DVT was similar (38% Ar SCVC, 36% AI SCVC); 62 DVT on SCVC in place, 7 after SCVC removal. Above-knee DVT occurred in 13 patients with SCVC-related DVT. Occlusion was higher with Ar SCVC (18% vs. 11%).
Timing of adverse effects: 65% of DVTs were diagnosed at first US examination, while 24% occurred with SCVC in place in 62 patients, while 7 DVTs were found 1 to 5 days after ablation of SCVC.
Factors that predict response: age >30 years and intracranial hypertension.

Source citation: Miyagaki et al. 2012[54]

Study Design: RCT
Device Material: PUR PICC (PI Catheter; Covidien) vs. silicone PICC (Groshong; Bard)

Contact Duration: Median dwell (days): 16 (range 5 to 52) PUR
Dose: Single lumen, 4 Fr
Frequency/ Duration: 1 attempt
Response: Hemorrhage, Occlusion, Phlebitis
Patient characteristics (gender, mean age): 96% male. 64.5 years PUR, 67 years Groshong.
Number per group: 14 PUR, 11 Groshong.
Observed adverse effects: Complications with PUR PICC included phlebitis (1), occlusion (2 (14.3%)), and hemorrhage (12). Hemorrhage (12 vs. 8) and occlusion (2 vs. 0) were higher with PUR PICC.
Timing of adverse effects: NR.
Factors that predict response: NR.

Source citation: Pittiruti et al. 2012[55]

Study Design: Retrospective controlled cohort
Device Material: Power-injectables PUR PICCs (brands NR)
Contact Duration: Mean dwell (days): 25±12
Dose: 50 triple-lumen 6 Fr, 21 double-lumen 5 Fr, 2 double-lumen 4 Fr, 16 single-lumen 4 Fr
Frequency/ Duration: 1 attempt
Response: CRT, Local hematoma, Malposition, Partial obstruction
Patient characteristics (gender, mean age): NR.
Number per group: 89 overall.
Observed adverse effects: 8 partial obstruction, 2 symptomatic catheter-related central venous thrombosis, 1 malposition, 3 (3.4%) local hematoma..
Timing of adverse effects: Thrombosis occurred within 10 days of insertion.
Factors that predict response: NR.

Source citation: Cohen et al. 2011[56]

Study Design: Retrospective controlled cohort
Device Material: PUR PICC (PowerHickman) vs. silicone PICC (Leonard); both Bard Access
Contact Duration: Mean dwell (days): 78 PUR
Dose: 9.5 Fr PUR, 10 Fr silicone; both dual-lumen
Frequency/ Duration: NR.
Response: Breakage, Malposition, Occlusion
Patient characteristics (gender, mean age): NR.
Number per group: 94 PUR, 117 silicone.
Observed adverse effects: Breakage was significantly lower with PUR (0% vs. 8%). Catheter removal due to mechanical failure (occlusion and malposition) was less frequent with PUR (5% vs. 8%).
Timing of adverse effects: NR.
Factors that predict response: NR.

Source citation: Nakae et al. 2010[57]

Study Design: RCT
Device Material: PUR VAC (Niagara Slim-Cath; Medicon)
Contact Duration: Dwell (days): 7 vs. 14
Dose: Double lumen
Frequency/ Duration: NR.
Response: DVT, Edema, Malfunction
Patient characteristics (gender, mean age): 84% men, 66.5 years.
Number per group: 29 1-week, 27 2-week (90 VAC: 48 1-week, 42 2-week).
Observed adverse effects: Complications in 2-week group included DVT and edema in 1 patient each. 6 catheters (3 each dwell time) were excluded from the study due to catheter dysfunction.
Timing of adverse effects: 1 week and 2 week.

Factors that predict response: NR.

Source citation: Ong et al. 2010[58]

Study Design: RCT
Device Material: Proximal valve PUR PICC (Vaxcel with PASV technology; Boston Scientific) vs. distal valve silicone PICC (Groshong; Bard)
Contact Duration: Mean dwell (days): 28.9 (range 2-245) PUR
Dose: 4 Fr; 17G PUR, 18G silicone
Frequency/ Duration: 1 attempt (286), 2 attempts (34), 3-4 attempts (11)
Response: Dislodgement, Fracture/leakage, Occlusion, Phlebitis
Patient characteristics (gender, mean age): PUR: 60% male, 49 years. Silicone: 66% male, 51 years.
Number per group: 198 PUR, 194 silicone.
Observed adverse effects: Incidence of phlebitis was significantly lower with PUR (11.6% vs. 23.2%). Other complications with PUR were occlusion (9.6%), fracture/leakage (1%), and dislodgment (2.5%); NS.
Timing of adverse effects: NR.

Factors that predict response: NR.*Estimated from Figure 1. allo-HSCT: allogeneic hematopoietic stem cell; CI: confidence interval; CICC: centrally inserted central catheter; cm: centimeter; CRT: catheter-related thrombosis; CVAD: central venous access device; CVC: central venous catheters; CVS/O: central venous stenosis/obstruction; DM: diabetes mellitus; DVT: deep vein thrombosis; ELT: ethanol lock therapy; Fr: French; G: gauge; IQR: interquartile range; LPC: long peripheral catheter; MC: midline catheter; mm: millimeter; NNT: number needed to treat; NR: not reported; NS: not significant; PASV: pressure activated safety valve; PICC: peripherally inserted central catheter; PIVC: peripheral intravenous catheter; PTFE: polytetrafluoroethylene; PUR: polyurethane; RA: right atrium; RCT: randomized controlled trial; SCVC: subclavian central venous catheter; SVC: superior vena cava; US: ultrasound; VAC: vascular access catheters; VT: venous thrombosis

Table 11: Intravascular Catheters – Health Effect (In Vivo) Animal Studies

Source citation: Teilmann et al. 2014[59]

Study Design: RCT
Device or Material: PUR catheter (MAC-13) vs. silicone (MAC-2BS); both SAI Infusion
Route: Subcutaneous
Dose: 1 Fr PUR in all catheters
Frequency/ Duration: 1 attempt
Response: Blood clot obstruction, Damaged catheter, Embolism
Species (strain): Mice (BomTac:NMRI)
Gender: Male.
Number per group: 13 PUR, 7 silicone.
Observed adverse effects: Complications with PUR catheters included embolism (4), blood clot obstruction (6; 1 mouse also had a damaged catheter), and damaged catheter (2).
Timing of adverse effects: Last day of patency for PUR catheters ranged from day 1 to day 25.
Factors that predict response: NR.

Table 5. Blood Access Devices – Health Effect (*In Vivo)* Human Studies

Source citation: Alzahrani et al. 2018[60]

Study Design: Controlled cohort study
Device Material: IVAP with a PU catheter; IVAP with a SiO catheter
Contact Duration: Mean: 2.95±1.61 years (PU catheter IVAP), 2.35±1.52 years (SiO catheter IVAP)
Dose: NR

Frequency/ Duration: Single IVAP administration in the supraclavicular region
Response: Catheter fracture, Catheter leakage, Thrombosis complications
Patient characteristics (gender, mean age): PU catheter IVAP: 51 female, 79 male, 7.76±3.69 years. SiO catheter IVAP: 29 female, 57 male, 12.64±5.23 years.
Number per group: PU catheter IVAP: 130, SiO catheter IVAP: 86
Observed adverse effects: There were no significant differences between the SiO group and the PU group according to IVAP indications ($p = 0.47$). No thrombosis complications were noticed in either group during the catheterization period. Catheter fractures occurred in 11/130 (8.5%) patients in the PU catheter IVAP group and 0/86 (0%) patients in the SiO catheter IVAP group ($p = 0.0083$ between groups).
Timing of adverse effects: PU catheter IVAP: mean 2.95±1.61 years, SiO catheter IVAP: mean 2.35±1.52 years.
Factors that predict response: For the PU catheter IVAP group, there were significant correlations between catheter fracture rate and the implantation duration ($p = 0.0001$) as well as catheter fracture rate and patient age ($p = 0.027$). The catheter fracture rate increased with patient age.

Source citation: Premuzic et al. 2018[61]

Study Design: Case series
Device Material: Permanent PU HC (Tesio Twin Catheter System)
Contact Duration: Mean: 8.5-27.8 months
Dose: NR
Frequency/ Duration: Single HC administration via internal jugular or femoral veins with catheter tip located in right atrium or other veins
Response: CVT, Catheter malfunction, Concentrations of C-reactive protein, fibrinogen, IgG and IgM cardiolipin antibodies, and platelets, Fibrin sheath formation, Positive for factor V Leiden and LAC
Patient characteristics (gender, mean age): 28 female, 40 male, 60.2±16.2 years.
Number per group: 68.
Observed adverse effects: For all of the 14 patients with the catheter tip located in the right atrium, there was no indication of CVT. CVT occurred in 31/68 (45.5%) patients with catheter tip located in other veins, including the SVC/IVC [26/31 (83.8%) patients] and smaller veins [5/31 (16.1%) patients]. 30/31 (96.8%) of patients with CVT had catheter tip location on the vein wall. Fibrinogen concentration and IgM cardiolipin antibodies were significantly higher in the CVT group than the no CVT group [37/68 (54.4%) patients]. There was a significantly greater number of patients with positive factor V Leiden mutation in the CVT group [11/31 (35.5%) patients] than the no CVT group [1/37 (2.7%) patients] ($p<0.05$ between groups).
Timing of adverse effects: Assessment period before HC exchange NR.
Factors that predict response: NR.

Source citation: Busch et al. 2017[62]

Study Design: Controlled cohort study
Device Material: IVAP PU catheter (Titanium SlimPort); IVAP SiO catheter (Cook Vital-Port Mini Titanium)
Contact Duration: > 30 days
Dose: 6.0 Fr PU, 5.0 Fr SiO
Frequency/ Duration: Single IVAP administration in the upper arm
Response: Catheter fracture, Infection, including local site infection and catheter-related sepsis, Other catheter malfunction, including catheter disconnection from IVAP, Thrombotic catheter occlusion, Venous thrombosis
Patient characteristics (gender, mean age): Cook Vital-Port Mini Titanium: 297 female, 241 male, 59.6 years, range: 19.5-88.5 years. Titanium SlimPort: 1,073 female, 659 male, 58.1 years, range: 18.2-91.7 years.
Number per group: Cook Vital-Port Mini Titanium: 538, Titanium SlimPort: 1,732.
Observed adverse effects: The total mean complication rate was 12.25% (Cook Vital-Port Mini Titanium: 14.87%; Titanium SlimPort: 11.43%; $p=0.040$). Infections occurred in 25/538 (4.64%) patients in the Cook Vital-Port Mini Titanium group and 81/1,732 (4.68%) patients in the Titanium SlimPort group ($p=1$ between groups). Thrombotic catheter occlusions occurred in 15/538 (2.79%) patients in the Cook Vital-Port Mini Titanium group and 23/1,732 (1.33%) in the Titanium SlimPort group ($p=0.035$ between groups). Venous thrombosis occurred in 4/538 (0.74%) patients in the Cook

Vital-Port Mini Titanium group and 55/1,732 (3.17%) in the Titanium SlimPort group (p=0.003 between groups). Catheter fractures occurred in 18/538 (3.36%) patients in the Cook Vital-Port Mini Titanium group and 1/1,732 (0.06%) in the Titanium SlimPort group (p<0.001 between groups).
Timing of adverse effects: Assessments between 1 and 4 days, and periodic assessments for more than 30 days.
Factors that predict response: NR.

Source citation: Ferraresso et al. 2016[63]

Study Design: Case series
Device Material: AVG (AVflo)
Contact Duration: Mean: 946±570 days
Dose: NR
Frequency/ Duration: Single AVG administration in the forearm (4 patients), upper arm (5 patients), or thigh (three patients)
Response: AVG kinking, Infection rate, Thrombosis complications, Thrombotic rate
Patient characteristics (gender, mean age): 5 female, 7 male, 68.5±10 years.
Number per group: 12.
Observed adverse effects: AVG kinking occurred in one patient. No infections or thromboses occurred as late complications. Two patients on post-implantation day 149 and 209, respectively, developed a stenosis of the venous outlet of the graft that was found to be neointimal hyperplasia.
Timing of adverse effects: 12 and 24 months.
Factors that predict response: NR.

Source citation: Kojima et al. 2016[64]

Study Design: Controlled cohort study
Device Material: IVAP PU catheter (Anthrone); IVAP SiO catheter (Gröshong X-port)
Contact Duration: Mean: 278 days (Anthrone), 425 days (Gröshong X-port)
Dose: 5 Fr PU, 8 Fr SiO
Frequency/ Duration: Single IVAP administration in the chest wall
Response: Catheter embolization, Total and partial catheter fracture rates
Patient characteristics (gender, mean age): Anthrone: 121 female, 100 male, 61.2±14.5 years. Gröshong X-port: 185 female, 199 male, 59.5±15.4 years.
Number per group: Anthrone: 221, Gröshong X-port: 384.
Observed adverse effects: Catheter fractures occurred in 16/384 (4.2%) patients in the Gröshong X-port group and 0/221 (0%) patients in the Anthrone group (p = 0.005 between groups).
Timing of adverse effects: Anthrone: mean 278 days, Gröshong X-port: mean 425 days.
Factors that predict response: The log-rank tests to determine the factors associated with fracture showed that smaller patient body mass index (p=.039), deeper catheter tip position (p=.022), and the SiO catheter (p=.019) were significantly associated with fracture.

Source citation: Wildgruber et al. 2016[65]

Study Design: Controlled cohort study
Device Material: IVAP PU catheter (Portolino); IVAP SiO catheter (Vital Mini Port)
Contact Duration: Mean: 264 days (Portolino), 344 days (Vital Mini Port)
Dose: Mean: 264 days (Portolino), 344 days (Vital Mini Port)
Frequency/ Duration: Single IVAP administration in the forearm (666 patients); Multi-IVAP administration in the forearm (15 patients)
Response: Catheter disconnection from IVAP, Catheter leakage, Catheter rupture, Catheter-tip thrombosis, CRBSI rate, Thrombosis of the catheter-carrying vein, Thrombophlebitis
Patient characteristics (gender, mean age): 472 female, 209 male, 58.3±12.0 years, range: 19-86 years.
Number per group: Portolino: 396, Vital Mini Port: 302.
Observed adverse effects: A total of 211 catheter-related complications in 146 patients were observed (1.0/1000 catheter days). 183 catheter-related complications occurred with the Portolino IVAP (1.7/1000 catheter days) and 28 occurred with the Vital Mini Port IVAP (0.3/1000 catheter days).

CRBSIs occurred in 30/396 (7.6%) patients in the Portolino group and 11/302 (3.6%) patients in the Vital Mini Port group (p=0.002 between groups). Catheter-tip thrombosis occurred significantly more frequently in the Portolino group (141/396, 35.6%) compared to the Vital Mini Port group (6/302, 2.0%), p<0.0001. Thrombosis of the catheter-carrying vein occurred in 7/396 (1.8%) patients in the Portolino group and 2/302 (0.7%) patients in the Vital Mini Port group (p=0.170 between groups).

Timing of adverse effects: Assessments between 1 and 12 days for both IVAP groups. Periodic assessments between 13 and 951 days (Portolino group) and 13 and 1228 days (Vital Mini Port group).

Factors that predict response: NR.

Source citation: Power et al. 2014[66]

Study Design: RCT
Device Material: Long-term PU HC (TesioCath); Long-term PU HC (Lifecath Twin)
Contact Duration: ≤ 12 months
Dose: 10 Fr
Frequency/ Duration: Single HC administration via right internal jugular vein
Response: Catheter displacement, Infection rate, including exit site and tunnel infections, Thrombotic catheter occlusion
Patient characteristics (gender, mean age): LifeCath Twin: 15 female, 26 male, 58.9±16.4 years. TesioCath: 10 female, 29 male, 63.3±15.6 years.
Number per group: LifeCath Twin: 41, TesioCath: 39.
Observed adverse effects: There were no significant differences between patient groups at the time of HC randomization nor was there a significant difference in patient survival between the two HC groups (p=0.65). Infections occurred in 12/41 (29.3%) patients in the LifeCath Twin group and 12/39 (30.7%) patients in the TesioCath group (p>0.05 between groups). Catheter displacement occurred in 1/41 (2.4%) patients in the LifeCath Twin group and 1/39 (2.6%) patients in the TesioCath group. Thrombotic catheter occlusions occurred in 2/41 (4.9%) patients in the LifeCath Twin group and 0/39 (0%) patients in the TesioCath group. Overall, there was no significant difference in HC survival between groups (p=0.5).
Timing of adverse effects: Assessments at 12 hours and three times a week between 1 and 52 weeks.
Factors that predict response: NR.

Source citation: Goossens et al. 2011[67]

Study Design: Systematic review
Device Material: PUR catheters (Chemosite, Port-a-cath, open PUR)
Contact Duration: Mean catheter days: 29.5 months (Vandoni),
Dose: NR
Frequency/ Duration: NR
Response: Obstructions, Occlusions
Patient characteristics (gender, mean age): Vandoni 2009: NR, 58 years. Ponnet 1997: NR, range 23 to 81 years.
Number per group: Vandoni: 228 TIVADs. Ponnet: 123 TIVADs.
Observed adverse effects: 1 RCT reported 11 catheter obstructions: 4 (5.1%) with Chemosite and 7 (9.2%) with Port-a-cath. 1 RCT reported an incidence of withdrawal occlusions of 6.5% of inserted open PUR catheters.
Timing of adverse effects: NR.
Factors that predict response: NR.

Source citation: Kakkos et al. 2011[68]

Study Design: Case control

Device Material: PUR vascular access graft (Vectra®) vs. carbon-impregnated PTFE vascular access graft (IMPRA® Carboflo®) all CR Bard
Contact Duration: NR
Dose: NR
Frequency/ Duration: NR
Response: Pseudoaneurysm
Patient characteristics (gender, mean age): 51% female, 63 (IQR 53 to 75) years. Number per group: 324 patients, grafts: 239 PUR, 126 PTFE.
Number per group: 324 patients, grafts: 239 PUR, 126 PTFE.
Observed adverse effects: Pseudoaneurysms (6 anastomotic, 30 needle-stick site) in 36 (9.9%) patients. 3-year pseudoaneurysm formation (at needle-stick site) was not significantly different (17% PUR, 23% PTFE; p=0.72). Occlusion was reported in 1 graft (type NR).
Timing of adverse effects: NR.
Factors that predict response: NR.

Source citation: Meier et al. 2011[69]

Study Design: RCT
Device Material: PUR catheter (sDLC; GamCath GDK-1320;) vs. surface modified DLC (smDLC; GamCath Dolphin® Protect 1320): all Gambro
Contact Duration: Dwell (hours): 149.4±51.3 sDLC, 141.6±49.7 smDLC
Dose: Double-lumen 13 Fr
Frequency/ Duration: NR
Response: Bleeding, Dysfunction, Hematoma, Kinking, Thrombotic events
Patient characteristics (gender, mean age): sDLC: 59% male, 58.4 year. smDLC: 57% male, 55.4 years.
Number per group: 118 patients each arm; 138 sDLC, 126 smDLC.
Observed adverse effects: Catheter dysfunction was significantly higher with PUR (14% sDLC, 5% smDLC). Significantly more thrombotic events occurred with PUR (4.2/1000 catheter days sDLC, 2.3/1000 catheter days smDLC; p=0.021). Kinking at insertion occurred in 2 PUR catheters. Local bleeding or hematoma complications were similar (number of events NR).
Timing of adverse effects: Dysfunction measured at 72 hours of CRRT.
Factors that predict response: NR.

Source citation: Power et al. 2011[70]

Study Design: Retrospective cohort
Device Material: PUR catheters (Bio-Flex Tesio Catheter (twin); MedCOMP)
Contact Duration: Mean followup (months): 23.8±23.3
Dose: NR
Frequency/ Duration: 1 attempt: 96%; 2 attempts: 4%
Response: Dislodgement, Dysfunction, Stenosis
Patient characteristics (gender, mean age): 57% male, 60 years.
Number per group: 433
Observed adverse effects: Central venous stenosis occurred in 22 (5%) patients. Dysfunction rate of 0.35 per 1,000 catheter days (95% CI: 0.31 to 0.41); 164/195 (84%) admissions related to dysfunction were due to suboptimal flow not resolved with catheter locks. Catheter dislodgement occurred in 31/759 (4%) patients.
Timing of adverse effects: NR.
Factors that predict response: NR.

Source citation: Bertoli et al. 2010[71]

Study Design: Case series
Device Material: Twin Tesio catheters (Gemini, Bellco)
Contact Duration: Mean followup (days): 248
Dose: 10 Fr, single-lumen, 70-cm long
Frequency/ Duration: 1 attempt
Response: Hematoma, Severe limb swelling, Soft tissue swelling, Thrombosis
Patient characteristics (gender, mean age): 52% female, 77.7 years.
Number per group: 25.
Observed adverse effects: Complications included 3 thrombosis (2 catheter tip thrombi, and 1 DVT), 8 (32%) hematomas, 2 (8%) soft tissue swellings around the tunnel. Severe limb swelling was observed in 1 patient without sign of vein thrombosis. No malfunctions were reported.
Timing of adverse effects: 6 and 12-month followup.
Factors that predict response: NR.

Source citation: Qureshi and Abid 2010[72]

Study Design: Case series
Device Material: PUR catheters (MedComp® and Arrow International®)
Contact Duration: Followup (months): 5
Dose: Double lumen
Frequency/ Duration: NR
Response: Erythema, Pain, Pus exudation, Tenderness
Patient characteristics (gender, mean age): 62% male, 48% >45 years, 51% <45 years.
Number per group: 60
Observed adverse effects: Local inflammation (pain, erythema, tenderness and pus exudation) at catheter site was observed in 19 (31.66%) patients.
Timing of adverse effects: NR
Factors that predict response: NR.

Source citation: Ravari et al. 2010[73]

Study Design: Controlled cohort study
Device Material: PUR grafts (Vasculink Co.) vs. PTFE grafts (Gore Co.)
Contact Duration: Followup (months): 24
Dose: 20 cm length, 8 mm diamete
Frequency/ Duration: NR
Response: Thrombosis
Patient characteristics (gender, mean age): PUR: 58% male, 61 years. PTFE: 48% male, 57 years.
Number per group: 50.
Observed adverse effects: Thrombosis occurred in 5 (20%) patients with PUR (12% with PTFE). Necrosis, pain, and steal syndrome were reported, but graft type was not identified.
Timing of adverse effects: NR.
Factors that predict response: NR.

AVG: arteriovenous graft; CI: confidence interval; cm: centimeter; CRBSI: catheter-related bloodstream infection; CRRT: continuous renal replacement therapy; CVT: central venous thrombosis; DLC: double lumen catheter; F: French; fCVC: femoral central venous catheters; HC: hemodialysis catheter; IgG: immunoglobulin G; IgM: immunoglobulin M; IQR: interquartile range; IVAP: implantable venous access port; IVC: inferior vena cava; LAC: lupus anticoagulant; mm: millimeter; NR: not reported; RCT: randomized controlled trial; PTFE: polytetrafluoroethylene; PU: polyurethane; PUR: polyurethane; sDLC: standard double lumen catheter; SiO: silicone; SVC: superior vena cava; TIVAD: totally implantable venous access devices

Table 12: Catheter Securement – Health Effect (In Vivo) Human Studies

Source Citation: Gravante et al. 2020 [74]

Study Design: Systematic review
Device or Material: 2 RCTs: BPD, SPD, TA with SPD, SSD with SPD; 1 RCT: PUR adhesive keyhole dressing (Veni-Gard) vs. additional PUR semipermeable transparent dressing (OpSite); 1 RCT: PUR transparent dressings vs. new-generation dressings (ADVANCED study)
Contract Duration: NR
Dose: NR
Frequency/ Duration: NR
Response:
PAC failure (composite outcome including complete dislodgement, occlusion, pain, local or blood infection; composite outcome including complete dislodgement, occlusion, phlebitis, infection)
Dysfunction (composite of complete dislodgement, accidental catheter removal, infection)
Patient characteristics (gender, mean age): NR, only adults included.
Number per group: Of the 4 RCTs reporting outcomes of interest, study enrollment ranged from 123 to 300.
Observations on adverse effects: 2 RCTs reporting composite PAC failure rates both indicated higher catheter failure with SPD vs. BPD (Edwards: 21% SPD, 5% BPD, 11% TA, 16% SSD; p=0.03 SPD vs. BPD)(Reynolds: 20% SPD, 13.3% BPD, 6.3% TA with SPD, 16.1% SSD with SPD). The ADVANCED study indicated dysfunction incidence rates of 12.9 per 1,000 catheter-days. Lastly, 1 RCT indicated that failure was highest with Veni-Gard vs. Veni-Gard plus Opsite (60% vs. 40%) with similar incidence of occlusion (50%).
Timing of adverse effects: NR.
Factors that predict response: NR.

Source Citation: Dang et al. 2019 [75]

Study Design: Network meta analysis
Device of Material: 13 antimicrobial dressings; SPU and BPU included PUR
Contract Duration: At least 48 hours (inclusion criteria)
Dose: NR
Frequency/ Duration: NR
Response: Catheter failure
Patient characteristics (gender, mean age): 49% male, NR.
Number per group: 35 RCTs (8494 patients); 8 RCTs reported catheter failure.
Observations on adverse effects: Statistically significant reduction in catheter failure with SSD vs. other dressings (OR 0.35, 95% CI: 0.14 to 0.89). Lowest to highest incidence of catheter failure (devices with PUR italicized): SSD, TD, SPU, SSD plus SPU, CHG, suture + AD, TA + SPU, BPU, SPU+BPU, TA, suture + BPU, ISD and SDG.
Timing of adverse effects: NR.
Factors that predict response: NR.

Source Citation: Dolcino et al. 2017 [76]

Study Design: Controlled cohort study
Device or Material: PUR CVC vs. silicone CVC; Group A (no use of SAS) vs. Group B (use of SAS); SAS devices included StatLock (Bard), Grip-Lok (Zefon), and SecurAcath (Interrad Medical)
Contract Duration: Mean dwell (days): 188±143
Dose: Mean Fr diameter: 6.08
Frequency/ Duration: 1 attempt: 80.3%, 2 attempts: 12.1%; >2 attempts: 7.5%
Response:
Dislodgements
Malfunction
Thrombosis
Patient characteristics (gender, mean age): 59.5% males, 72.32 months.
Number per group: 95 PUR, 78 silicone. PUR made up 54.9% of all catheters. 42% of Group A, and 86% of Group B.
Observations on adverse effects: Complications included 27 dislodgements (25 in Group A, 2 in Group B), 4 thrombosis (3 in Group A, 1 in Group B), and 6 malfunctions (5 in Group A, 1 in Group B).
Timing of adverse effects: NR.

Factors that predict response: NR.

AD: adherent dressing; BPD: bordered PUR dressing; BPU: bordered PUR dressing; CHG: chlorhexidine gluconate-impregnated dressing; CVC: central venous catheter; Fr: French; ISD: integrated securement dressing; NR: not reported; OR: odds ratio; PAC: peripheral arterial catheter; PUR: polyurethane; RCT: randomized controlled trial; SAS: subcutaneously anchored securement; SDG: sterile dry gauze; SPD: standard PUR dressing; SPU: standard PUR dressing; SSD: sutureless securement device; TA: tissue adhesive; TD: transparent dressing

Table 13: Cardiovascular Pacemaker Electrode – Health Effect (In Vivo) Human Studies

Source citation: Debski et al. 2018[77]

Study Design: Retrospective Cohort
Device Material: Lead insulation: Silicone PU 80A, PU 55D
Contact Duration: Mean: 73.2 months
Dose: Average 2 leads per patient
Frequency: Single operation
Response: Lead dislodgement, Cardiac perforation, Lead failure
Patient characteristics (gender, mean age): 53.4% male, 46.6% female, mean 69.8 years old
Number per group: 3771 patients total, 38 leads with PU 80A insulation, and 14 leads with PU 55D insulation, the rest is silicone insulation
Observed adverse effects: Lead failures is the primary observation. For PU80A insulation, 11 of 38 (28.9%) leads failed. For PU55D, none of the 14 leads failed
Timing of adverse effects: NR
Factors that predict response: Atrial lead position, subclavian vein access, unipolar lead construction, and PU 80A insulation.

Source citation: Forleo et al. 2014[78]

Study Design: Prospective Cohort
Device Material: Lead insulation: Silicone-polyurethane copolymer (Optim)
Contact Duration: Mean:
25.7 months
Dose: Average 1.8 leads per patient
Frequency: Single operation
Response: Lead dislodgement, Lead failure
Patient characteristics (gender, mean age): 196 males, 34 females, 67.5 years old
Number per group: 413 leads in 234 patients
Observed adverse effects: Of the 413 Opti P m-coated leads, 4 (1%) had dislodgement, and 7 (1.7%) had electrical lead failure
Timing of adverse effects: NR
Factors that predict response: NR

Source citation: Kolodzinska et al. 2012[79]

Study Design: Case series
Device Material: Lead insulation: PU or silicone
Contact Duration: Mean: 82.2 months
Dose: Average 1.9 leads per patient
Frequency: Average 2 operations per patient
Response: Severe insulation damage
Patient characteristics (gender, mean age): 12 female, 19 males, 70.4 years old
Number per group: 56 leads from 31 patients
Observed adverse effects: Severe insulation damage in the intracardiac part was present in 8/26 silicone-insulated leads and 5/5 with PU overlay (P = 0.004)
Timing of adverse effects: Removed leads with PU overlay were younger (mean implantation time 35.8+2 months) than silicone-insulated ones (mean implantation time 91.2+2 months) (P = 0.0007)
Factors that predict response: NR

PU: Polyurethane; PEU: polyether polyurethane; NR: Not reported.

Table 14: Ventricular Assist Devices – Health Effect (In Vivo) Human Studies

Source citation: Beiras-Fernandez et al. 2013[80]

Study Design: Case series
Device Material: Polyurethane valves inside the Excor ventricle
Contact Duration: NR
Dose: 1 biventricular support (Excor; Berlin Heart) per patient
Frequency: Single operation
Response: Thrombosis
Patient characteristics (gender, mean age): NR; NR
Number per group: 2 patients
Observed adverse effects: 6 thrombi were found across the 2 patients
Timing of adverse effects: 5 and 7 days respectively
Factors that predict response: Heparin/platelet factor 4.

NR: Not reported;

Table 15: Ventricular Assist Devices – Health Effect (In Vivo) Animal Studies

Source citation: Mizuno et al. 2011[81]

Study Design: Single case
Device or Material: Polyurethane skin button
Route: Subcutaneous skin implant
Dose: 1 implant
Frequency/ Duration: Single operation/90 days
Response: Gross findings. Inflammation. Granulomas
Species (strain): Calf
Gender: NR
Number per group: 1 animal
Observations on adverse effects (brief): No gross findings like infection or inflammation were observed. No traumatic injury observed. Granuloma showed mature formation
Timing of adverse effects: 90 days
Factors that predict response: NR
Data Quality: NR.

NR: Not reported;

Table 16: Neurostimulation Devices – Health Effect (In Vivo) Animal Studies

Source citation: Rao et al. 2012[82]

Study Design: Comparative
Device or Material: PDMS miniature rod with and without PEG containing PU hydrogel coating

Route: Cortical implants
Dose: 1 implant per animal
Frequency/ Duration: Six weeks
Response: GFAP immunoreactivity, NeuN immunoreactivity
Species (strain): Sprague-Dawley rats
Gender: All male
Number per group: 18.
Observations on adverse effects (brief): PU-coated implant group demonstrated significantly lower GFAP immunostaining intensity, suggesting fewer astrocytes (an indication of immunoreaction). NeuN immunostaining assess neuronal survival neared the implants, which showed the PU-coated group with significantly higher NeuN signal. Overall, PU coating demonstrates better biocompatibility than the uncoated control.
Timing of adverse effects: 6 weeks
Factors that predict response: NR.

PDMS: polydimethylsiloxane; PEG: polyethylene glycol; PU: polyurethane; GFAP: glial fibrillary acidic protein; NeuN: neuron-specific nuclear protein; NR: Not reported

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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.