MEDICAL DEVICE MATERIAL PERFORMANCE STUDY

Polymethyl methacrylate Safety Profile

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Executive Summary

Key Points

1. Searches identified 1523 citations; 37 articles were selected for inclusion
2. When used in bone cement, PMMA does not appear to cause local toxicity, although the use of bone cement beads may be related to some rare events such as allergies, mechanical complications, increased antibiotic resistance, and thromboembolic complications. Current evidence suggests that PMMA in bone cement does not cause systemic toxicity. The quality of evidence related to local responses and systemic responses are moderate and low, respectively.
3. When used in orthopedic components, the evidence is limited but suggests that PMMA does not cause local toxicity (with no evidence on whether it causes systemic toxicity). Accordingly, the quality of evidence for both toxicity responses is very low.
4. When used in ocular implants, PMMA in some devices (ICRS, Boston type I KPro, capsular tension rings [CTRs] for cataract surgery) are associated with various local host responses, but most studies are uncontrolled, so the causal contribution of PMMA is unclear and the quality of evidence is very low. When used in intraocular lenses (IOLs) for cataract surgery, controlled studies suggest that PMMA does not cause local toxicity (moderate quality of evidence). For systemic toxicity, KPro implant may increase serum tumor necrosis factor (TNF) levels, indicating a possible response to ocular inflammation.
5. For dermal fillers, there is moderate evidence that local toxicity risks include long-term inflammatory response (granulomas, swelling, redness, or lumpiness). There is evidence that a systemic risk is injection-associated hypercalcemia, but the quality of evidence is very low.
6. PMMA in dental material can potentially cause allergic dermatitis in patients or dentists or dental technicians, but other dental materials were also associated with allergic reactions, so the unique contribution of PMMA is unclear. There were no studies that investigated systemic toxicity.
7. PMMA for cranioplasty can cause infection, but evidence is conflicting and the quality is very low. There were no studies that investigated systemic toxicity.
8. The accident investigation and Problem Reporting Network (PRN) data on PMMA devices is limited. Accident investigations concluded that user error and improper cleaning of instrumentation lead to the adverse events. The PRN report indicated that a patient died 5 minutes after bone cement injection during a kyphoplasty.
9. Patient Safety Organization (PSO) data included 1 report of infection associated with a dental implant categorized as a harm-score-indicating error, but caused no harm to the patient.
10. The Healthcare Technology Alerts database returned the most relevant results (28 alerts). These consisted of instructions for use (IFU) and labeling recalls, but also more serious hazards primarily associated with bone cements. More serious hazards include failure to meet sterility requirements, visible particles on implant surface, and cement clumping.
11. Evidence gaps:
    a. No included studies investigated PMMA as a material. Additional human and animal studies are indicated.
    b. Many identified human studies lacked comparison groups, making it difficult to determine whether complications are directly associated with the device material. More studies comparing PMMA devices to control groups of different materials are indicated.
    c. Randomized controlled trials (RCTs) are needed to confirm the trend that PMMA antibiotic-loaded spacers (ALSs) used prior to the implantation of orthopedic implants do not elicit local and systemic responses compared to implants without spacers.
    d. RCTs that compare PMMA to various materials (e.g., titanium) used for cranioplasty specifically designed to investigate local and systemic responses to the material by precluding complications known to occur during the procedure are also needed.

Overview - Polymethyl Methacrylate (PMMA)

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 5 key questions provided by FDA and summarized below, regarding a host's local and systemic response to PMMA. 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 PMMA?

In human studies, PMMA appears to cause local toxicity in some devices but not others (see specific responses/events under 1a. below). The available ECRI surveillance data were related, in part, to component separation, improper instrumentation cleaning, and failure to meet sterility requirements. However, it was unclear in the data whether 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. No local toxicity for bone cement overall, but bone cement beads may cause some rare events, and bone cement for femoral nails may cause thrombosis.
ii. No local toxicity for orthopedic components.
iii. For IOLs, no additional complications. For ocular implants, ICRS are associated with epithelial defects, white deposits, corneal thinning, infective keratitis, and edema; Boston type I KPro IOLs are associated with retroprosthetic membrane, glaucoma, vitreoretinal complications, keratolysis, uveitis; CTRs are associated with posterior capsule opacification.
iv. For dermal filter, inflammatory response.
v. For dental materials, allergic dermatitis in patients or dentists or dental technicians.
vi. For cranioplasty, infection.

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

i. The time course for intracorneal ring segment (ICRS) responses varied depending on the complication and study reporting. White deposits were noted as early as 3 weeks, corneal thinning and melting were observed from 24 to 48 weeks, and infectious keratitis anywhere from 26 weeks to 240 weeks after surgery.
ii. Retroprosthetic membrane formation and glaucoma after Boston type I KPro IOL insertion can be seen as early as 6 months after surgery and have been noted 2 and 5 years postsurgery.
iii. Posterior capsule opacification was seen as early as 12 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?

Four studies/reviews reported data on systemic signs/symptoms of PMMA devices

b. What are the likely systemic manifestations?

For bone cement, no systemic toxicity for PMMA in femoral nails.
For Boston type I KPro, increased serum TNF.
For dermal filler, injection-associated hypercalcemia.

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

Increased serum TNF levels were seen at a mean 5.3 ± 3.7 years after KPro surgery.
Onset of hypercalcemia from initial injection was a mean 7.96 ± 7.19 years.

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

None of the studies identified cellular/molecular mechanisms.

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?

The included studies reported the following information about possible patient-related factors that may influence the risk of local toxicity of PMMA devices:

- For bone cement, Zhang et al. 2020[1] found that greater osteoporosis was associated with a greater risk of screw loosening.
- For orthopedic components, Staats et al. 2017[2] found that the presence of ALS led to a reduced rate of reinfection (local toxicity).
- For ocular implants, de la Paz et al. 2019[3] reported that patients with chemical injuries or autoimmune diseases affecting the eye had a higher incidence of retroprosthetic membrane (RPM) formation.
- For ocular implants, Talati et al. 2018[4] stated "Although this study is not powered to completely exclude an effect of titanium in RPM formation, our results support the findings of Rudnisky et al. and suggest that host factors play a more critical role than the backplate material in the pathophysiology of the RPM." Specifically, patients with preoperative diagnoses of bullous keratopathy, aniridia, uveitis, and cicatricial conjunctivitis had a higher incidence of RPM formation in both titanium and PMMA backplate groups.
- For ocular implants, Al Arfaj et al. 2015[5] reported that "preoperative conditions such as autoimmune diseases, chemical injury, LSCD [limbal stem cell deficiency], deep corneal vascularization were found to be associated with studies reporting lower retention rates."
- For ocular implants, Lee et al. 2015[6] reported that complications increase for eyes "predisposed to inflammatory effects around the back plate of the KPro device."
- For ocular implants, Sanghi et al. 2011[7] found no difference in the inflammation and postoperative complications in children 3 years and younger vs. those older than 3 years.
- For cranioplasty, Leao et al.[8] suggested various patient factors that are related to higher infection rates due to technical errors in surgery are potentially related to patients with hypertension, diabetes, systemic infection, lower hemoglobin levels, and motor deficits.

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?

The included studies reported the following information about possible material-related factors that may influence the risk of systemic toxicity of PMMA devices:

- For ocular implants, Hennig et al. 2014[9] found that "The increased risk of capsule opacification [PCO] in rigid PMMA IOLs can be reduced by a square edge design of the optic."
- For ocular implants, Todani et al. 2011[10] found a higher rate of RPM with screw-on PMMA backplate (46%) than with snap-on PMMA backplate (31%) and this difference was not statistically significant.
- For dermal fillers, Paulucci 2020 [11] reported that the risk of inflammation was related to the use of needle vs. cannula as well as "features of the vehicle" and "product origin."
- For cranioplasty, Las et al. 2021[12] reported that incomplete resin polymerization can release residual monomers that increase cytotoxicity.

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

All gaps listed here could benefit from future research.

a. No included studies investigated PMMA as a material. Additional human and animal studies are indicated.
b. Many identified human studies lacked comparison groups, making it difficult to determine whether complications are directly associated with the device material. More studies comparing PMMA devices to control groups of different materials are indicated.

c. RCTs to confirm the trend that PMMA ALS used in orthopedic implants do not elicit local and systemic responses compared to implants without spacers are needed.
d. RCTs that compare PMMA to various materials (e.g., titanium) used for cranioplasty specifically designed to investigate local and systemic responses to the material by precluding complications known to occur during the procedure are needed.

Project Overview

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

1. Magnesium (Mg)
2. Complications Associated with Polypropylene Mesh in Pre-, Peri-, and Post-Menopausal Women
3. Polytetrafluoroethylene (PTFE)
4. Acrylics: Polymethyl Methacrylate (PMMA)
5. Acrylics: Poly (2-hydroxyethyl methacrylate) (pHEMA)
6. Acrylics: Cyanoacrylates (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 PMMA?
    a. *Can that response vary by location or type of tissue the device is implanted in or near?*
    b. *Over what time course does this local host response appear?*
2. Does the material elicit a persistent or exaggerated response that may lead to systemic signs or symptoms – beyond known direct toxicity problems?
    a. *What evidence exists to suggest or support this?*
    b. *What are the likely systemic manifestations?*
    c. *What is the observed timeline(s) for the systemic manifestations?*
    d. *Have particular cellular/molecular mechanisms been identified for such manifestations?*
3. Are there any patient-related factors that may predict, increase, or decrease the likelihood and/or severity of an exaggerated, sustained immunological/systemic response?
4. Are there any material-related factors that may predict, increase, or decrease the likelihood and/or severity of an exaggerated, sustained immunological/systemic response?
5. What critical information gaps exist, and what research is needed to better understand this issue?

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

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

Literature Search and Systematic Review Framework

The ECRI-Penn Evidence-based Practice Center (EPC) conducts research reviews for the Agency for Healthcare Research and Quality (AHRQ) Effective Health Care (EHC) Program. ECRI's scientific staff within our Center for Clinical Excellence has authored hundreds of systematic reviews and health technology assessments on 3,500+ technologies/interventions for ECRI's

public- and private-sector clients. In addition to this work, ECRI staff have coauthored several methods papers on evidence synthesis published on the AHRQ Effective Health Care website and in peer-reviewed journals.

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

- **Material Response**
  - Strength
  - Embrittlement
  - Degradation
  - Migration
  - Delamination
  - Leaching
- **Host Response**
  - Local
    - Inflammation
    - Sensitization
    - Irritation
    - Scarring/fibrosis
      - *Keloid formation*
      - *Contracture*
    - Ingrowth
    - Erosion
  - Systemic
    - Cancer
      - *Lymphoma*
    - Inflammation
    - Immune Response
    - Fatigue
    - Memory Loss
    - Rash
    - Joint Pain
    - Brain Fog

Search strategies were developed for each concept and combined using Boolean logic. Several search approaches were used for comprehensiveness. Strategies were developed for devices of interest as indicated by FDA as well as the material-related strategies. Each of these sets were combined with the material and host response strategies. Detailed search strategies and contextual information are presented in Appendix B. Text mining, logistic regression, and a search for "random" and "systematic" in titles and abstracts were used to prioritize only the top 35%-40% of the identified literature. This subset was screened against the inclusion criteria, first by title/abstract review, and then by full article review. An evidence prioritization scheme was used to ensure the inclusion of no more than 50 studies. Data were extracted from the resulting articles.

ECRI Surveillance Search Strategy

There are 4 key ECRI sources for medical device hazards and patient incidents. These databases were searched by key terms and device models. Relevant data were extracted to address the key questions agreed upon by FDA and ECRI. Patient

demographics were extracted when available. All data presented were redacted and contain no protected health information (PHI).

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

ECRI Patient Safety Organization (PSO)

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

Full Name: Poly methyl methacrylate
CAS Registry Number: [9011-14-7]

Safety Brief - Systematic Review Results

The systematic review included clinical and engineering literature on biocompatibility (i.e., host response and material response) of poly methyl methacrylate (PMMA) used in medical devices. In addition to fundamental material biocompatibility, we focused on specific devices known to be made of PMMA. 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 PMMA provided by FDA to Guide ECRI Searches

Regulatory Description	Product Code	Class
Polymethyl methacrylate (PMMA) bone cement	LOD	2
PMMA bone cement, vertebroplasty	NDN	2
PMMA bone cement, antibiotic	MBB	2
PMMA bone cement, bone cement, posterior screw augmentation	PML	2
Methyl methacrylate for cranioplasty	GXP	2
Plate, cranioplasty, preformed, non-alterable	GXN	2
Plate, cranioplasty, preformed, alterable	GWO	2
Ring, endocapsular	MRJ	3
Eye sphere implant	HPZ	2
Implant, dermal, for aesthetic use	LMH	3
Prosthesis, knee, patellofemorotibial, semiconstrained, cemented, polymer/metal/polymer	JWH	2
Prosthesis, knee, femorotibial, semiconstrained, cemented, metal/polymer	HRY	2
Prosthesis, hip, semiconstrained, metal/polymer, cemented	JDI	2
Hip joint femoral (hemi-hip) metallic cemented or uncemented prosthesis	JDG	2
Hip joint metal/polymer/metal semiconstrained porous-coated uncemented prosthesis	LPH	2
Shoulder joint metal/polymer nonconstrained cemented prosthesis	KWT	2
Prosthesis, hip, semiconstrained, metal/ceramic/polymer, cemented or nonporous, uncemented	LZO	2
Prosthesis, hip, hemi-, femoral, metal/polymer, cemented or uncemented	KWY	2
Prosthesis, shoulder, semi-constrained, metal/polymer cemented	KWS	2
Prosthesis, knee, patellofemorotibial, semiconstrained, metal/polymer, mobile bearing	NJL	3
Keratoprosthesis, permanent implant	HQM	2
Intraocular lens	HQL	3
Lens, multifocal intraocular	MFK	3

Lens, intraocular, phakic	MTA	3
Denture, plastic, teeth	ELM	2

The Safety Brief summarizes the findings of the literature search on toxicity/biocompatibility of PMMA. 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 PMMA in various device categories.

Table 2: Summary of Primary Findings from our Systematic Review

Application	Local Host Responses/Device Events	Quality of Evidence (local responses)	Systemic Responses	Quality of Evidence (systemic responses)
Bone Cement	No local toxicity overall, but bone cement beads may cause some rare events, and bone cement for femoral nails may cause thrombosis.	Moderate for no local toxicity overall, and very low for bone cement beads and bone cement for femoral nails	No systemic toxicity for PMMA in femoral nails (no other PMMA bone cement was investigated for systemic responses.	Low
Orthopedic Components	No local toxicity	Very low	No studies	Very Low (no studies)
Ocular Implants / IOL	Intracorneal ring segments (ICRS): epithelial defects, white deposits, corneal thinning, infective keratitis, edema Boston type I KPro: retroprosthetic membrane, glaucoma, vitreoretinal complications, keratolysis, uveitis CTRs: posterior capsule opacification IOLs: no additional complications	ICRS and Boston type I KPro and CTRs: Very low IOLs: Moderate	Boston type I KPro: increased serum TNF	Low
Dermal Filler	Inflammatory response	Moderate	Injection-associated	Very Low

Application	Local Host Responses/Device Events	Quality of Evidence (local responses)	Systemic Responses	Quality of Evidence (systemic responses)
			hypercalcemia	
Dental	Allergic dermatitis in patients or dentists or dental technicians	Low	No studies	Very Low (no studies)
Cranioplasty	Infection	Very Low	No studies	Very Low (no studies)

PMMA as a Material

None of the included studies investigated PMMA as a material.

Bone Cement

Eight human studies (3 systematic reviews [SRs], 3 randomized controlled trials [RCT], and 2 nonrandomized comparative studies). For more information, see Table 1 in Appendix D.

Local Responses/Device Events (human studies)

One SR examined complications reported in studies of cement-augmented pedicle screws in patients with vertebral fractures or degenerative spinal disease.[1] The SR included 20 studies (1,654 patients) with only 2 studies being prospective. Local complications that may be related to bone cement included screw loosening 2.0% (95% confidence interval [CI] 0.2%–4.9%), screw breakage 0.6% (95% CI 0%–2.0%) and screw migration 0.2% (95% CI 0%–1.2%). The SR did not compare augmented to nonaugmented screws.

One SR examined complications reported in studies of antibiotic-impregnated bone cement beads used mostly for osteomyelitis and orthopedic prosthetic infections.[13] The SR included 275 studies with 208 articles published on PMMA beads. PMMA-related complications were reported mostly in case studies of rare events including allergies, mechanical complications related to damage to a bowel or vein in close proximity to the bead chain, and increased antibiotic resistance in organisms grown off of PMMA beads that were retained for an extended time.

One SR examined whether routine use of antibiotic-loaded bone cement helped reduce infection rates in primary total joint replacement and the risks associated with this approach.[14] The SR pooled data from 7 studies (88,258 patients) and made no mention of bone cement toxicity.

One RCT examined total knee replacement with and without bone cement in 77 patients.[15] After 11 to 15 years, patients with cemented tibial components had significantly more radiolucent lines beneath the tibial components, indicating separation and mechanical loosening. The study reported collecting data on complications but did not report whether any occurred.

One RCT examined femoral nails used to close trochanteric fractures with and without bone cement in 213 patients.[16] By 12 months, 4 augmented patients and 1 nonaugmented patient reported thromboembolic complications, and no augmented patients and 1 non-augmented patient reported hypersensitivity or allergy. The authors noted that no local soft tissue reactions related to cement application were reported in their study.

One RCT examined total knee arthroplasty with and without bone cement in 60 patients.[17] The only adverse events were not directly related to bone cement and no revisions were needed for aseptic loosening after 5 years. The study's adverse events section did not mention any local or systemic responses related to the use of bone cement.

One nonrandomized comparative study compared titanium-coated cementless implants with cemented implants in 81 patients undergoing total knee arthroplasty.[18] At 5 years, postoperative complications were similar.

One retrospective comparison study compared bone cement with bone graft material to repair benign locally aggressive and/or low grade malignant bone lesions in 36 pediatric patients.[19] Complication rates for reoperation, growth deformities, and postoperative pain were similar, but the study did not mention any local reactions to the bone cement.

Systemic Responses (human studies)

One SR examined complications reported in studies of cement-augmented pedicle screws in patients with vertebral fractures or degenerative spinal disease.[1] The SR included 20 studies (1,654 patients) with only 2 studies being prospective. Symptomatic cement leakage risk was 1.2% (95% CI: 0.6%–1.9%) and pulmonary embolism risk was 3.0% (95% CI: 0.5%–6.8%) using pooling data from 11 studies with 1,158 patients. Symptomatic pulmonary embolism risk was 0.8% (95% CI: 0.2%–1.5%).

An RCT[16] reported that systemic/rest of body complications were similar between the 2 groups (42% in noncemented and 43% in cemented), suggesting that bone cement does not cause systemic toxicity.

Overall Quality of Evidence

Four studies found that bone cement does not cause local toxicity. Two RCTs[16,17] each found no local toxicity events in either the cement group or the uncemented group. Two nonrandomized comparative studies[18,19] found similar rates of local toxicity. The quality of evidence is moderate, due to the consistency of findings and that 2 of the 4 studies had employed randomization.

Device events that could potentially be related to bone cement include screw loosening, screw breakage, and screw migration, and these are all rare (2% or less). The quality of evidence is low since the underlying studies in this SR were retrospective and likely not controlled.

Bone cement beads may be related to some rare events such as allergies, mechanical complications related to damage to a bowel or vein in close proximity to the bead chain, and increased antibiotic resistance in organisms grown off of PMMA beads. The quality of evidence is very low since the findings from this SR were based on mostly case studies.

Thromboembolic complications may occur when using bone cement for femoral nails, but this is only a single RCT and the rates in both groups were very low (5 events total out of 213 patients). One SR examining pedicle screws (20 studies and 1,654 patients) reported that symptomatic pulmonary embolism risk was only 0.8%. However, the SR included only 2 prospective studies out of 20, meaning that 18 studies were retrospective with a high risk of bias. The quality of evidence is very low.

Regarding systemic toxicity, an RCT using femoral nails[16] with and without bone cement found similar rates of systemic/rest of body complications (42% vs 43%), suggesting that bone cement does not cause systemic toxicity. The quality of evidence is low, and additional studies are needed to verify this finding.

Orthopedic Components

Three human studies, all nonrandomized comparative studies. For more information see Table 2 in Appendix D.

Local Host Responses (human studies)

One nonrandomized comparative study (n = 13 total) compared total hip arthroplasties via Girdlestone surgery with and without PMMA antibiotic-loaded spacer (ALS) with 8 g of vancomycin. [20]. These procedures are performed to treat existing infections associated with implants. For all cases, there was no infection recurrence or emerging infection surrounding the prostheses during the follow-up period (mean of 24 months). There were also no cases in either group of prosthesis loosening, dislocation, or a fracture around the prosthesis. There were two cases of poor wound healing, neither of which occurred in patients receiving PMMA spacers.

One nonrandomized comparative study (n = 46 total) compared 2-stage total hip revision arthroplasties with PMMA ALS to no spacers. The PMMA antibiotic bone cement contained 0.5 g of gentamicin and 2 g of vancomycin.[2] The study reports the occurrence of revision surgery due to infection recurrence. Kaplan–Meier analysis revealed a revision-free survival in the non-ALS group of 76.1% (n = 16) at 12 months, 71.4% (n = 15) at 24 months and a revision-free survival rate of 66.6% (n = 14) at 36 months. The group with ALS implantation showed a revision-free survival rate of 100% (n = 25) at 12 months, 100% (n = 25) at 24 months, and 92% (n = 23) at 36 months. The study investigated neither local toxicity nor systemic toxicity of the PMMA spacers.

One retrospective nonrandomized comparative study (n = 21 total) compared shoulder arthroscopy with PMMA ALS (with 0.5 g gentamycin) to no spacers in 21 patients (10 received ALS, and 11 received no spacer).[21] At follow-up (mean of 22 months), 2 patients without spacers had low-grade infections (between-group difference not statistically significant). The study

investigated neither local toxicity nor systemic toxicity of the PMMA spacers. Two patients who received PMMA spacers had other events: one fell and had a fracture near the spacer and the other had a fracture around a stemmed spacer (cause of fracture not reported).

Systemic Responses

No identified studies investigated systemic responses to PMMA orthopedic components.

Overall Quality of Evidence

For local toxicity, none of the 3 studies reported any local toxicity associated with PMMA orthopedic components, however they were not designed to detect such toxicity. All 3 compared the use of a PMMA spacer to no spacer, thus none isolated the effect of PMMA. The quality of evidence is very low.

For systemic toxicity, none of the 3 studies investigated it, so the quality of evidence is very low.

Ocular Implants / Intraocular lenses (IOL)

Sixteen human studies (8 SRs, 1 RCT, 7 nonrandomized comparative studies). For more information, see Table 3 in Appendix D.

Local Host Responses (human studies)

One SR examined intracorneal ring segments (ICRSs), all made of PMMA, and reported the following postoperative complications: migration, ring extrusion, corneal thinning, corneal melting, and infective keratitis.[22] The SR included 39 studies with 1,946 patients (2,590 eyes) and a 57-week mean follow-up. No non-PMMA ICRSs were examined, so a direct link to PMMA as a substance causing these complications cannot be made.

A second SR examined ICRSs, referred to as intrastromal corneal ring (ICRs) in this publication, reported the following complications: white deposits (5.75%) and epithelial defects (5.65%) in ICRS-only patients; and edema (5.08%), perforation (0.59%), and extrusion (0.59%), in patients with ICRS and corneal cross-linking.[23] The SR included 18 articles totaling 1,325 eyes with 12-month follow-up. According to the authors, complications are linked mainly to the construction of the tunnel for device placement. No non-PMMA ICRSs were examined, so a direct link to PMMA as a substance causing these complications cannot be made.

One SR examined the Boston type I keratoprosthesis (KPro) IOL and reported the following postoperative complications: retroprosthetic membrane (RPM) in 29 studies (36.6%); 39.3% for glaucoma, 27.5% for vitreoretinal complications, and 14.5% for keratolysis in 19 studies; incidence of endophthalmitis across 11 studies was 6.1%; 8.9% for sterile vitritis/uveitis and 7.6% for hypotony/phthisis across 9 studies.[24] The SR included 30 studies with 1,482 patients (1,619 eyes) and a 2- to 5-year follow-up. Authors noted the lack of high-quality evidence (all but 1 study was a cohort study) and the need for further research. A second SR also examined Boston KPro and reported that RPM occurred in 1% to 65% (30.0 ± 19.0% in 13 studies with follow-up of 6 to 47 months).[6] Glaucoma occurred in 2.4% to 64.0% with a follow-up of 6 to 47 months. The authors noted "The potential for complications increases with time after BI-KPro surgery and with eyes that are predisposed to inflammatory effects around the back plate of the KPro device."

One SR examined Boston KPro use in countries with harsher climatic conditions and reported that RPM affected 12% to 67% of eyes (7 studies with 657 eyes).[5]

One SR examined the Boston type I KPro in 100 patients with corneal blindness secondary to severe chemical ocular injury and reported the following postoperative complications: corneal necrosis/melt/thinning in 22.6%, RPM in 20.6%, glaucoma progression in 13.7%, extrusion in 11.8%, retinal detachment in 7.8%, and epithelial defect in 5.9%.[25] The mean follow-up was 25 months with a range of 5 to 98 months. Most studies were retrospective cohort studies.

One SR examined studies of Boston KPro and repeat penetrating keratoplasty (PK), reporting data on glaucoma and infection; all studies were case series.[26] The SR reported glaucoma in 25% of PK patients (n = 542, follow-up 9 to 72 months) and infectious keratitis in 18% (n = 362, follow-up 25 to 72 months). Among KPro patients (n = 98) 7.9% and 13.5% required glaucoma surgery at 2 and 5 years, respectively. In KPro patients, the infectious keratitis rate was 2.9% at 5 years. The authors noted "Although KPro surgery was once considered a last-resort procedure owing to its side effect profile of glaucoma and infection, new designs and better postoperative management have led to more encouraging outcomes."

One SR examined modified capsular tension rings (CTRs) used during cataract surgery and reported the following complications: posterior capsule opacification (PCO) (25.6% in 196 adult eyes and 74.7% in 91 pediatric eyes), and intraocular pressure spikes in 18 cases.[27] The mean follow-up range in included studies was 13 to 48 months.

One SR examined postoperative complications using various IOL types in cataract surgery.[28] Both acrylic and PMMA IOLs were compared but only 4 RCTs involving 216 participants (range of 2 to 140 participants with uveitic cataract per trial) were included in the SR. The authors noted "These studies, including a combined total of 16 participants with uveitis, were insufficiently powered to detect differences in outcomes among eyes of people with uveitis randomized to receive [heparin-surface modification] PMMA IOLs when compared with fellow eyes receiving unmodified PMMA IOLs." No statistically significant differences in outcomes were seen between eyes receiving heparin-surface modification PMMA IOLs and eyes receiving PMMA IOLs. The authors stated "At this time, there is not enough data to conclude whether additional types of lenses are preferable to other types."

An RCT compared flexible, hydrophilic acrylic IOLs (589 eyes) with rigid PMMA IOLs (611 eyes).[9] After 1 year, elevated intraocular pressure and uveitis were not reported in either group. PCO was significantly more common in the rigid PMMA IOLs (164 versus 99, $p<0.001$). The authors noted that the increase PCO risk with PMMA IOLs was due to their not having a square edge design which was present in the acrylic IOLs.

A prospective nonrandomized comparative study compared flexible, hydrophobic acrylic posterior chamber intraocular lens (PCIOL) with rigid PMMA PCIOL; 50 eyes in each group.[29] After 35 days, no statistically significant differences in postoperative complications were noted between groups. Edema was the most common complication and occurred in 4% of the acrylic group and PMMA group.

A prospective nonrandomized comparative study compared rigid heparin surface-modified PMMA IOLs (19 eyes) with foldable acrylic IOLs (23 eyes) in pediatric patients undergoing cataract surgery.[7] Follow-up was 1 to 5 years. The authors noted that inflammatory reactions and postoperative complications are low even with rigid IOLs when patients were treated after surgery with a single intravenous bolus of hydrocortisone and dexamethasone.

A retrospective nonrandomized study compared Boston type 1 KPro (n = 25) with a biological KPro (n = 45).[3] All patients had chemical injuries or autoimmune diseases affecting the eye. RPM formation and glaucoma were higher in the Boston KPro group compared to the biological group, but the differences were not significant. Median follow-up period was 0.1 to 8.8 years for the KPro group and 0.1 to 30.3 years for the biological group.

A retrospective matched comparison study examined KPros using titanium (n = 20) or PMMA backplates (n = 20).[4] The authors reported no significant difference in RPM development after 12 months (11 titanium and 6 PMMA eyes developed a visually significant RPM). The study authors suggested that host factors played a more important role in RPM development than the backplate material.

A retrospective comparison study compared Boston type I KPro using a titanium backplate (23 eyes) with a KPro using a PMMA backplate (16 snap-on and 39 screw-on).[10] At 6-month follow-up the screw-on PMMA backplate had the highest RPM incidence (46.1%) compared with 31.2% for the snap-on and 13% for the titanium backplate. The combined PMMA eyes had significantly more RPM than the titanium group ($p = 0.014$). The authors concluded that titanium caused less postoperative reaction than PMMA.

A retrospective comparison study compared cataract surgery with and without capsular tension rings (CTRs); 26 eyes with CTRs and 26 eyes without.[30] Mean follow-up was 24 months with CTRs and 28 months without CTRs. CTRs reduced long-term postoperative complications including secondary cataracts and capsular contraction syndrome.

Systemic Responses

A prospective nonrandomized comparative study compared patients implanted with the Boston type I KPro (n = 31) patients not implanted with the device (n = 34).[31] Mean time from KPro surgery to blood sampling was 5.3 years. Serum tumor necrosis factor (TNF)-α and TNF receptor 2 (TNFR2) levels were significantly elevated in KPro patients. The elevated levels remained significant after adjustment for glaucoma, IOP, body mass index, gender, and race. The authors noted that TNF is an inflammatory cytokine and elevated TNF levels may reflect TNF upregulation in response to ocular inflammation.

Overall Quality of Evidence

Across specific devices, 2 events (RPM and glaucoma) were mentioned in 5 or more studies/reviews. Nine events (corneal thinning, corneal melting, epithelial defects, extrusion, edema, infective keratitis, sterile vitritis/uveitis, posterior capsule

opacification, intraocular pressure increase) were mentioned in 2 studies/reviews. Thirteen other events were each mentioned only in a single study (ring extrusion, ring extrusion, corneal necrosis, white deposits, perforation, vitreoretinal complications, keratolysis, endophthalmitis, hypotony/phthisis, retinal detachment, inflammatory reactions, secondary cataracts, capsular contraction syndrome). Below, we discuss the evidence in 4 categories: ICRS, Boston type I Kpro, CTRs, and IOLs.

The use of ICRSs are associated with various local host responses including epithelial defects, white deposits, corneal thinning, infective keratitis, and edema as noted in 2 SRs.[22,23] The SRs examined only PMMA ICRS and therefore no clinical evidence from these publications directly links PMMA to local host responses. Both SRs noted that surgical trauma may be responsible for postsurgical complications such as corneal melting and better surgical technique would reduce complications. The quality of evidence is very low because there are no control groups, thus one cannot determine what event rates would have been observed if patients had not received these devices.

The use of Boston type I KPro IOLs is associated with various local host responses including RPM, glaucoma, vitreoretinal complications, keratolysis, and uveitis as noted in several SRs.[5,6,24,26] No non-PMMA KPros were examined in these SRs, so one cannot determine whether PMMA caused these complications. A retrospective comparative study of KPro with a non-PMMA KPro device indicated that RPM development was similar regardless of material composition.[3] Two retrospective comparisons of KPros with PMMA and titanium backplates found conflicting results. One reported no differences in RPM development, and the other concluded PMMA was responsible for a higher incidence of RPM.[4,10] The quality of evidence is very low because there were no control groups in the SRs, and the controlled studies were retrospective.

CTRs used during cataract surgery are associated with PCO according to one SR.[27] Similar to the other SRs no non-PMMA devices were included in the analysis. A retrospective comparative study reported the use of CTRs reduced long-term postoperative complications indicating CTRs were not responsible for local responses.[30] The quality of evidence is very low because there were no control groups in the SR and the controlled study was retrospective.

IOLs used in cataract surgery are available in PMMA and non-PMMA acrylics, and studies comparing these lenses may provide evidence on local responses specifically to PMMA. A SR of 4 RCTs did "not have sufficient data to conclude whether additional types of lenses are preferable to other types."[28] Three studies (1 RCT and 2 nonrandomized comparative studies) reported similar rates of inflammatory reactions and postoperative complications when comparing flexible, hydrophilic acrylic IOLs with rigid PMMA IOLs,[9] hydrophobic acrylic PCIOL with rigid PMMA PCIOL,[29] and rigid heparin surface-modified PMMA IOLs with foldable acrylic IOLs.[7] The similar rates suggest that PMMA does not cause additional complications. The quality of evidence is moderate that using PMMA as a material for IOLs does not cause additional complications.

For systemic toxicity, 1 prospective study indicates that the KPro implant may increase serum TNF levels, indicating a possible response to ocular inflammation. The quality of evidence is low since this is a single small nonrandomized study and the finding needs to be verified with additional studies.

Dermal filler

Three human studies (2 SRs and 1 RCT). For more information, see Table 4 in Appendix D.

Local Host Responses (human studies)

One SR analyzed published literature on the frequency of granuloma and other complications following injection of PMMA facial fillers.[11] The SR identified 5 articles including 1,842 patients, and also included many case reports. Most commonly reported adverse events were persistent swelling or redness, lumpiness at the injection site. and granuloma or enlargement of the implant. Complication rates ranged from 3% to 10% depending on the reviewed study. 55% of all reported adverse events occurred within the first year of implant. An additional 35% of reported adverse events occurred up to 5 years after the injection (10% at year 2, 10% at year 3, 5% at year 4, and 10% at year 5). These data indicate that the chronic inflammatory response to PMMA injection may be active for years after injection. The primary chronic adverse event was formation of granulomas. The authors postulated that potential triggers of inflammatory response are primarily dependent on the specific filler product and how the filler is delivered to the patient's skin. Potential triggers include product origin, volume and concentration of injected filler, size of microspheres, area/ depth of filling, and provider experience.

One RCT compared the adverse events associated with PMMA dermal fillers to saline injection (control) at a 2:1 ratio (96 PMMA filling and 49 saline injections).[32] Each PMMA patient received 2 administrations of a mean PMMA dosage of 0.11 mL per facial scar with a maximum administration of 5.8 mL per session. Mean follow-up time was 6 months, and most reported

adverse events were minor and reversible (swelling and tenderness, rates not reported) that often manifested and resolved in 2 days. No significant differences in efficacy or safety were noted between genders, skin types, or age.

Systemic Responses

One SR analyzed published literature on cosmetic injection-associated hypercalcemia (potential life-threatening heightened levels of calcium.[33] The authors identified 23 patients from 20 articles. Cosmetic injection materials included silicone (43.5%), PMMA (30.4%; 7 of 23 patients who had hypercalcemia) and paraffin oil (8.7%). Injection sites were buttocks (69.5%) and breast (39.1%). Results of this SR did not report material-specific incidents of hypercalcemia. As an aggregate, hypercalcemia developed at a mean duration of approximately 8 years with renal failure being the most common complication (82% of cases) leading to 2 deaths.

Overall Quality of Evidence

Inflammatory response is a risk of PMMA dermal fillers, based on evidence from a systematic review of 5 articles (over 1,800) patients. Such responses take the form of granulomas, swelling, redness, or lumpiness at the injection site, and events can occur up to 5 years after the injections. One RCT found results conflicting with the conclusions from the SR. Overall, the quality of the evidence is moderate for local inflammatory responses from PMMA dermal fillers.

Regarding systemic responses to PMMA dermal fillers, one SR identified 7 patients from 20 articles who had experienced injection-associated hypercalcemia. Given the low number of patients and the uncertain causal connection between PMMA and hypercalcemia, the quality of the evidence is very low.

Dental

Two human studies (1 SR, 1 nonrandomized comparative study). For more information, see Table 5 in Appendix D.

Local Host Responses (human studies)

One SR analyzed published literature to develop a systematic approach for the selection and monitoring of dental materials available in the market to predict their risk of inducing allergic reactions.[34] The SR identified 71 relevant articles (60 case reports, 8 prospective studies, and 3 retrospective studies). Ten studies that reported allergic reactions to PMMA dentures were included. Two studies reported a 1% prevalence of contact allergy to methyl methacrylate among dental professionals due to repeated exposure. Two different studies describe methods to reduce leachable substances from acrylic dentures, thus reducing potential allergic reactions. These methods include submersion of the dentures in hot water (50˚C) for 1 hour or exposure to ultraviolent light before inserting the dentures into the oral cavity. Another study reported allergic contact stomatitis experienced by a patient with mild erythema in the gingiva and buccal mucosa.

One nonrandomized comparative study of dentures compared adverse events after administrating soft relining PMMA material to vinyl-polysiloxane (16 PMMA, 11 vinyl-polysiloxane).[35] After 3 years, patients completed a questionnaire. For both groups, all patients stated that the retention and stability of dentures improved and no adverse events were reported.

Systemic Responses

No identified studies investigated systemic responses to PMMA dental products.

Overall Quality of Evidence

PMMA in dental material can potentially cause allergic dermatitis in patients or dentists or dental technicians, as reported in 10 studies from a systematic review. Other dental materials also were associated with allergic reactions, so the unique contribution of PMMA is unclear. A separate study reported no adverse events. Overall, the quality of evidence for allergic dermatitis is low.

Neither study investigated systemic toxicity, so the quality of evidence is very low.

Cranioplasty

Five human studies (1 nonrandomized comparative study, 4 SRs). For more information, see Table 6 in Appendix D.

Local Host Responses (human studies)

One SR analyzed studies that identified toxic (aseptic) reactions to any types of material used as cranioplasty implants or onplants, including PMMA.[12] Follow-up time ranged from immediately after surgery to 45 years. In 11 studies (164 patients), 11% of patients (18 patients) experienced PMMA-related toxicity. Four patients presented hypersensitivity and allergic reaction (1 death), 8 patients experienced chronic aseptic inflammation, and 6 patients experienced neurotoxicity. The SR determined that, of the identified studies reporting toxicity reactions to specific materials, 11% subjects presented toxicity reactions to PMMA (n = 164, 11 studies), 2.9% subjects presented toxicity reactions to titanium (n = 209, 3 studies), and 0.8% subject presented toxicity reactions to calcium phosphate (n = 394, 3 studies).The SR states "for acrylic-based materials (polymer or PMMA), residual monomer generates toxicity. In vitro studies have demonstrated the cytotoxic effects of the PMMA monomer. The number of residual monomers formed, and the subsequent level of cytotoxicity, relate to the method of polymerization."[12]

One SR analyzed studies comparing complication rates of PMMA to autologous bone and to titanium mesh cranioplasty implants.[8] The SR included 11 articles (1,256 patients) with a follow-up range of 63 days to 54.3 months. Of the analyzed materials, autologous bone presented a complication rate of 17.44% , PMMA of 14.1%, titanium of 8.6%, ceramic of 5.88%, hydroxyapatite of 32.5%, and PMMA + titanium of 0%. This SR found that no statistical differences were observed in the complication rates between autologous bone and PMMA or between titanium mesh and PMMA. Among all complications (n = 205), infection was the most prevalent (113; 55.1%), followed by hematoma (36; 17.5%), dehiscence (17; 8.2%), seroma (9' 4.4%), material displacement (7; 3.4%), thermal sensitivity (2; 1%), bone resorption (2; 1%), and edema (1; 0.5%). No difference was observed between the complication rates of PMMA and autologous bone (p = 0.94; RR, 0.98; 95% CI 0.54–1.75) or between PMMA and titanium (p = 0.38; RR, 1.59; 95% CI 0.57–4.48).

One SR analyzed studies comparing infection rates with titanium mesh, PMMA, polyether ether ketone (PEEK), and Norian cranioplasty implants. The SR included 53 articles and 3,591 patients (1,429 titanium, 1,459 PMMA, 221 PEEK, 482 Norian). Follow-up time was not clearly reported but studies with follow-up times less than 12 months were excluded. The SR concluded that PMMA implants were associated with a statistically significantly higher infection rate than other implant types (7.95% vs. 6.05%, p = 0.0266). The authors were unable to stratify calculations by age, sex, severity of injury, comorbidities, and other variables that may serve as factors that predict response.

One SR analyzed studies comparing clinical outcomes of 3D-printed, custom-made cranial implants composed of PMMA, titanium mesh, PEEK, and hydroxyapatite (HA).[36] The SR reviewed 27 studies including 1,688 implants (649 titanium, 298 PMMA, 233 PEEK, 508 HA); 348 complications were recorded in 1,688 patients (20.64%) with 210 surgical revisions. Postoperative fluid collection was less likely with PMMA (0.34%) than with other materials (2% to 6%). However, PMMA had a slightly higher rate of postoperative infection (10.5%) than other materials (7.3% to 10.2%) and also a slightly higher rate of the need for second surgery for postoperative infection (10.1% PMMA vs. 6% to 7.7% for other materials). PMMA showed a lower rate of postoperative epidural hematoma (0.68% compared to 2.8% to 4.62% for other materials) compared with other materials.

One nonrandomized comparative study compared adverse events associated with cranioplasty reshape implants composed of PMMA to those composed of titanium.[37] The study included 120 patients (60 PMMA, 60 titanium) with a mean follow-up time of approximately 200 days. There was no significant difference of adverse events between groups. Incidents of infection (PMMA = 6, titanium = 5), hemorrhage (PMMA = 6, titanium = 4) and cerebrospinal fluid (CSF) fistula (PMMA = 3, titanium =2) were all comparable. In the PMMA group, one patient experienced tissue necrosis and another patient experienced neuropathy.

Systemic Responses

No identified studies investigated systemic responses to PMMA cranioplasty implants.

Overall Quality of Evidence

Four SRs and 1 nonrandomized comparative study compared complication rates of various materials used for cranioplasty. Two found higher rates of infection with PMMA materials than other materials; however, another found no difference in overall complication rates, and the other did not statistically compare infection rates. The extent to which PMMA actually causes infection is unclear, since patients receiving PMMA cranioplasty may have been more susceptible to infection or the PMMA devices may have been implanted at institutions with relatively ineffective infection protocols. The nonrandomized comparative study was too small to permit clear conclusions about comparative infection rates. Due to study designs and inconsistency and imprecision, the overall quality of evidence about infection is very low.

One of the systematic reviews reported other events including hypersensitivity and allergic reaction, chronic aseptic inflammation, and neurotoxicity, but these were all relatively rare. Due to a lack of reporting by other reviews and studies, the overall quality of evidence about these events is very low.

ECRI Surveillance Data

ECRI surveillance database searches were guided by the terms listed in Appendix F. The accident investigation and PRN data on PMMA devices included 2 reports involving bone cement and 1 report involving IOLs. One AFI investigation concluded that extraneous bone cement broke off of a knee prosthesis and became localized debris leading to premature joint failure. The other investigation reviewed several incidents of patient's suffering toxic anterior segment syndrome (TASS) following cataract surgery at one location over a 5 month period. It was concluded that improper instrument disinfection techniques caused TASS and that it was not directly related to the various implanted IOLs models. The PRN reports a patient suffering cardiac arrest and dying shortly after receiving a cement injection during a 3-level kyphoplasty procedure. The PSO data included 1 report of infection associated with a dental implant categorized as a harm score of C, indicating error, but no harm to the patient. The Healthcare Technology Alerts database returned the most results (28 alerts). These consisted of instructions for use (IFU) and labeling recalls, but also more serious hazards primarily associated with bone cement. More serious hazards include failure to meet sterility requirements, visible particles on implant surface, and cement clumping.

Patient Safety Organization

Search Results:

ECRI PSO identified 623 reports that involved PMMA materials that occurred between 4/2015 and 11/2020. 1 of these involved a complication.

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

Table 3: : Complications in PMMA-related PSO event reports

Complication	Dental Implant	Total
Infection	1	1
Total	**1**	**1**

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

	Harm Scores (NCC-MERP)	Dental Implant	Total
A	No Error		
B1	Error, No Harm		
B2	Error, No Harm		
C	Error, No Harm	1	1

	Harm Scores (NCC-MERP)	Dental Implant	Total
D	Error, No Harm		
E	Error, Harm		
F	Error, Harm		
G	Error, Harm		
H	Error, Harm		
I	Error, Death		
NULL*			
Total			1

**Harm score was not reported*

Accident Investigations

Search Results: 2 investigations were recovered and are summarized in Table 5.

Table 5: Accident Investigations of Patient Incidents Involving PMMA-related Devices

Device Type	# Investigations	Reported Problem and Findings
Bone Cement	1	Failure of knee prosthesis. Suspected extraneous bone cement left around the prosthesis joint broke loose and became debris within the articulating surfaces, contributing to wear and joint failure.
Intraocular lenses	1	Incidents of toxic anterior segment syndrome (TASS) following cataract surgery.

These investigations are redacted and included in Appendix F.

ECRI Problem Reports

Search Results: The search returned 1 report submitted by an ECRI member.

Key Issues: The report detailed cardiac arrest and death.

Safety Concerns: The report states that the patient went into cardiac arrest 5 minutes after the third bone cement injection.

Table 6: ECRI Problem Report Summary

Device Type	# Problem Reports	Reported Problem and ECRI Findings
Bone cement (NDN)	1	Death occurred 5 minutes after injection of cement on a 3-level kyphoplasty. After third bone cement injection, patient went into cardiac arrest.

All problem reports are redacted and included in Appendix F

Healthcare Technology Alerts

Search Results: The search returned 28 manufacturer-issued alerts describing problems with labeling, packaging, IFU updates, no FDA clearance, failure to meet sterility requirements, inclusion of incorrect components, cement clumping, implant loosening, unanticipated performance, missing markings, and particles on implant surface, summarized in Table 7.

Table 7: Summary of Regulatory and Manufacturer Alerts

Device Type	# Alerts	Reported Problem
LOD (PMMA bone cement); MBB (Antibiotic PMMA bone cement)	13 Manufacturer-issued	• Packaging issue • Mislabeling • Increased histamine levels (post-op complications) • Failure to meet sterility requirements • Not cleared for indicated use • Cement clumping • Unanticipated performance
LOD (PMMA bone cement)	1 Manufacturer-issued	• Mislabeling
NDN (vertebroplasty PMMA bone cement)	1 Manufacturer-issued	• Updated IFU
LOD (PMMA bone cement); NDN (vertebroplasty PMMA bone cement)	2 Manufacturer-issued	• Failure to meet sterility requirements • Updated IFU
JWH (prosthesis, knee, P-F, semiconstrained, cemented, poly/metal/poly)	1 Manufacturer-issued	• Particles on implant surface
HRY (orosthesis, knee, F-T, semiconstrained, cemented, metal/poly)	1 Manufacturer-issued	• Implant loosening
JDG (prosthesis, hip, femoral, cemented, metal)	2 Manufacturer-issued	• Mislabeling • Missing component
JDG (prosthesis, hip, femoral, cemented, metal); NJL (prosthesis, knee, P-F, semiconstrained, metal/poly, mobile)	1 Manufacturer-issued	• Particles on implant surface
JDI (prosthesis, hip, semiconstrained, metal/poly, cemented)	4 Manufacturer-issued	• Mislabeling • Packaging issues • Failure to meet sterility requirements • Missing markings

Device Type	# Alerts	Reported Problem
LZO (prosthesis, hip, semiconstrained, metal/ceramic/poly, cemented or non-porous, uncemented)	1 Manufacturer-issued	• Mislabeling
JDI (prosthesis, hip, semiconstrained, metal/poly, cemented); LPH (prosthesis, hip, semiconstrained, metal/poly, porous, uncemented); LZO (prosthesis, hip, semiconstrained, metal/ceramic/poly, cemented or nonporous, uncemented)	1 Manufacturer-issued	• Packaging issues

Potential Gaps

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

PMMA as a Material

None of the included studies investigated PMMA as a material. Because of this, additional research that focuses primarily on the biocompatibility of PMMA is indicated.

Bone Cement

There is moderate evidence (2 RCTS and 2 nonrandomized comparative studies) indicating that no local host response is associated with PMMA bone cement. However, more research is indicated to investigate systemic responses to PMMA bone cement, with only 1 systematic review signifying a low risk of complications (cement leakage and pulmonary embolism) associated with pedicle screws and an RCT suggesting that bone cement does not cause systemic toxicity.

Orthopedic Components

Overall, there is an evidence gap related to both local and systemic host responses to orthopedic components composed of PMMA. All 3 human nonrandomized comparative studies compared joint replacements (2 hip, 1 shoulder) with ALS to those without spacers and did not identify any statistically significant differences in complication rates between the 2 groups. However, neither local nor systemic toxicity were directly investigated, indicating additional research is needed to directly investigate whether the use of PMMA ALS may lead to local host responses or systemic toxicity.

Ocular Implants / Intraocular Lenses (IOL)

Overall, there is an evidence gap related to both local and systemic toxicity responses to ocular implants composed of PMMA. All SRs that investigated ICRSs, Boston type I KPro, and CTRs lacked control groups. Therefore, although complications and local host responses were identified, it is not possible to determine whether PMMA caused these complications. Moreover, for Boston type I KPro, 2 retrospective comparisons had conflicting results when comparing PMMA and titanium backplates. Only

1 study indicated a systemic response to the KPro implant in that the implant may increase TNF levels that may serve as a marker for ocular inflammation. Additional research that includes control groups are indicated to determine whether PMMA is the cause of the complications noted in these studies.

Dermal Filler

Only 1 SR and 1 RCT investigated local host responses to dermal fillers. The SR concluded that PMMA dermal fillers can lead to the formation of granulomas and that chronic inflammatory responses can persist for years while the RCT found no difference in complication rates between PMMA fillers and saline injections. One SR investigated cases of hypercalcemia associated with dermal fillers composed of different materials. However, the report did not provide a material-specific analysis. More research is needed to confirm whether PMMA dermal fillers potentially cause a prolonged inflammatory response as well as investigate any systemic toxicity responses.

Dental

There is low evidence of allergic reactions to PMMA dentures by both patients and healthcare workers handling the dentures. No studies investigated systemic responses. Overall, more research is needed to investigate potential local host and systemic toxicity responses to PMMA dentures.

Cranioplasty

Four SRs and 1 nonrandomized comparative study compared complication rates of various materials used for cranioplasty. However, the study designs and presentation of results make it difficult to determine whether reported complications are related to the material or complications that occurred during or directly after the surgical procedure. More research is indicated to specifically study the local and systemic responses to PMMA associated with cranioplasty.

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

Inclusion Criteria

1	English language publication
2	Published between January 2010 and January 21, 2021
3	Human studies
4	Systematic reviews, randomized controlled trials, cohort studies, case-control studies, cross-sectional studies, case series
5	Studies that evaluate toxicity/biocompatibility of PMMA 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 providing relevant data.
3.	**Consistency of data** – are the findings consistent across studies that report relevant data?
4.	**Magnitude of effect** – what is the likelihood of adverse effects compared to controls (with no device, lower dosage, shorter exposure time), and possibly number of patients likely to have harms.
5.	**Directness of evidence** – do human studies isolate the effect of the device (i.e. can the adverse effects be attributed to the device)?
6.	Is there evidence of a **dose response or time response** (e.g. adverse effects increase with longer exposure time)?

Appendix B. Search Summary

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

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

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

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

Literature Search for Polymethylmethylacrylate (PMMA)

Set Number	Concept	Search Statement
Material		
1.	PMMA	'poly(methyl methacrylate)'/exp OR 'acrylic acid methyl ester'/exp OR 'methacrylic acid methyl ester'/exp OR 'methacrylic polymer*' OR 'polymethylmethylacrylat*' OR 'polymethylmethacrylat*' OR 'polymethylmetacrylat*' OR 'polymethyl methylacrylat*' OR 'polymethyl methacrylat*' OR 'polymethyl metacrylat*' OR 'poly methyl methylacrylat*' OR 'poly methyl methacrylat*' OR 'poly methyl metacrylat*' OR 'polybutylmethacrylat*' OR 'polybutyl methacrylat*' OR 'poly butyl methylacrylat*' OR 'poly butyl methacrylat*' OR ((polymethyl OR butyl OR polybutyl) NEAR/2 acrylat*) OR pmma OR pbma
2.	PMMA Trade Names	acrypol OR acrypet OR acrycon OR acrylite OR acryplen OR acryrex OR akrylon OR callocryl OR carboset OR colacryl OR ivocap OR 'sr-ivocap' OR meliodent* OR paladent OR palapress OR paladur OR palaxpress OR palamat OR palajet OR palabond OR palaseal OR 'onda cryl' OR 'qc 20'
3.	PMMA devices: Simplex cements	('simplex p' OR 'simplex hv' OR 'simplex mv' OR 'simplex ro' OR 'simplex t' OR 'simplex r' OR (simplex AND (antibiotic* OR bone OR cement OR radiopaque OR tobramycin OR gentamicin OR surgical OR powder OR stryker))) NOT ('simplexvirus'/exp OR 'herpes simplex')

4.	PMMA devices: Other bone cements	'antibiotic bone cement'/exp OR 'antibiotic bone cement'/syn OR 'affirm vcf':ti,ab,dn,tn OR bonos:ti,ab,dn,tn OR 'biomet bone cement':ti,ab,dn,tn OR cemex:ti,ab,dn,tn OR 'cobalt'/dn OR 'cobalt bone cement':ti,ab,dn,tn OR 'cobalt g':ti,ab,dn,df OR 'cobalt hv':ti,ab,dn,tn OR cobalthv:ti,ab,dn,tn OR cobaltg:ti,ab,dn,tn OR 'cmw*':dn OR 'boneloc':ti,ab,dn,tn OR 'cranioplast':ti,ab,dn,tn OR 'cranioplexx':ti,ab,dn,tn OR 'osteobond':ti,ab,dn,tn OR 'vertebroplastic' OR 'depuy cmw' OR 'depuy gentamicin' OR 'kyphx*':ti,ab,dn,tn OR 'kyphon hv*':ti,ab,dn,tn OR 'xpede':ti,ab,dn,tn OR 'activos':dn OR 'mendos spine':ab,ti,dn,tn OR osteopal*:ti,ab,dn,tn OR palacos*:ti,ab,dn,tn OR palamed*:ti,ab,dn,tn OR refobacin:ti,ab,dn,tn OR 'spine-fix':dn OR smartset:ti,ab,dn,tn OR smartmix:ti,ab,dn,tn OR traumacem:ti,ab,dn,tn OR versabond*:ti,ab,dn,tn OR vertaplex*:ti,ab,dn,tn OR vertecem*:ti,ab,dn,tn OR vertefix*:ti,ab,dn,tn
5.	PMMA devices: Dermal filler	artefill OR bellafill OR arteplast OR artecoll
6.	PMMA devices: Eye implants	'intrastromal corneal ring segment'/dv OR 'intrastromal corneal ring segment' OR 'capsular tension ring'/dv OR 'capsular tension ring*' OR 'morcher ctr' OR 'ophtec ctr' OR 'symblepharon ring*' OR 'keraring*' OR 'intacs' OR 'intralase' OR 'myoring*' OR 'verisyse' OR 'auro kpro' OR 'auro k pro' OR 'aurokpro' OR 'b kpro' OR 'bi kpro' OR 'boston keratoprosth*' OR 'boston kpro*' OR 'boston type i*' OR 'boston type 1*' OR 'boston type 2*' OR 'm kpro'
7.	PMMA devices: Orthopedic/cranial components	'interspace':dn OR 'interspace knee' OR 'interspace shoulder' OR 'interspace hip' OR 'spacer k' OR 'spacer g' OR 'spacer s' OR septopal OR 'vancogenx' OR 'space knee' OR 'space hip' OR (('stage one' OR 'stageone') AND spacer*) OR anatomicsacrylic* OR cranioplastic*
8.	Combine and Limit by language and publication date	(#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7) AND [english]/lim AND [2011-2021]/py
9.	Limit by publication type	#8 NOT ('book'/it OR 'chapter'/it OR 'conference abstract'/it OR 'conference paper'/it OR 'conference review'/it OR 'editorial'/it OR 'erratum'/it OR 'letter'/it OR 'note'/it OR 'short survey'/it OR 'tombstone'/it)
Material Response		
10.		'biocompatibility'/de OR biocompat* OR tribolog* OR 'bio compat*' OR 'biological* compat*' OR 'biological* evaluation'
11.		'degradation'/exp OR degrad* OR adsorbable OR split* OR wear OR deteriorat* OR atroph* OR migrat* OR distend* OR distension OR 'delamination'/exp OR delamina* OR leach* OR filter* OR seep* OR evaginat* OR subsidence OR 'glistening*' OR 'nanoglistening*' OR 'whitening' OR discolor* OR opacificat*
12.		Leachable* OR extractable*
13.		(swell* OR shrink* OR contract* OR stretch* OR retract* OR extension OR extend* OR deform* OR creep OR plasticity OR degrad* OR disintegrat* OR fail* OR fragment* OR debond*) NEAR/3 (implant* OR prosthes* OR prosthetic* OR spacer? OR centralizer? OR plug? OR plate? OR cement? OR filler? OR denture? OR crown? OR bridge?)
14.		'mechanics'/exp
15.		'device material'/exp/mj
16.		'Biomedical and dental materials'/exp/mj

17.	Combine sets	#10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16
18.	**PTFE + Material Response**	**#9 AND #17**
Host Response		
19.		Host NEAR/2 (reaction* OR response*)
20.		'toxicity'/exp OR toxic*:ti OR cytotox* OR teratogenic* OR genotox* 'carcinogenicity'/exp OR carcinogen*:ti
21.		'immune response'/exp OR 'immunity'/exp/mj OR 'hypersensitivity'/exp OR 'immunopathology'/exp/mj
22.		(immun*:ti OR autoimmun*:ti OR hypersens*:ti) NOT immunofluorescenc*:ti
23.		'inflammation'/exp OR inflamm* OR 'arachnoiditis'
24.		'foreign body' OR granuloma* OR 'foreign body'/exp
25.		'adhesion'/exp OR 'tissue adhesion'/exp OR 'tissue response'
26.		protrude* OR protrus* OR perforat*
27.		'fibrosis'/exp OR 'capsul* contract*':de OR 'corneal melting'/exp OR 'sterile keratolysis' OR 'retroprosthetic membrane'/exp OR (retroprosth* NEAR/2 membrane) OR (fibro* NEAR/2 capsule*) OR 'astrocytosis'/exp OR 'gliosis'/exp
28.	Combine sets	#19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27
29.	Combine sets **PMMA + Material Response+ Host Response**	#18 AND #28
30.	**PMMA devices + Host response**	#9 AND (#3 OR #4 OR #5 OR #6 OR #7) AND (#19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27)
31.	**Final set**	**#29 OR #30**

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

I. 1523 citations identified by searches
   a. **933 citations not screened manually due to likely irrelevance** (based on text mining, logistic regression, etc.)
   b. 590 articles selected for title/abstract screening:
      - 457 selected by text mining in Distiller (30%)
      - 76 by logistic regression (5%)
      - 4 by the searcher for possible relevance
      - 53 for including "random" or "systematic in the title or abstract

      i. **335 citations excluded at the title/abstract level**

      Citation excluded at this level were off-topic, or not published in English, or did not address a Key Question, or did not report a device of interest, or did not report an outcome of interest

      ii. 255 full length citation

         1. 66 citations excluded at the full article level

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

         2. 189 citations reviewed for evidence prioritization

            a. 152 citations excluded at the prioritization level

            Citations excluded at this level were animal studies (8), single-arm studies (128), or RCTs (4) and nonrandomized comparative studies (12) whose comparison did not address the effect of PMMA

            b. 37 citations included

Appendix D. Evidence Tables

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

Local Response/Toxicity

Source Citation: Hampton et al. 2020[15]

Study Design: Randomized controlled trial
Device or Material: Cemented and noncemented components of a total knee replacement
Contract Duration: 11 to 15 years
Dose: NR
Frequency/Duration: Single administration
Response:

- Radiolucent lines
- Other complications

Patient characteristics (gender, mean age): Cemented: 63 years, 49% male
Uncemented: 64 years, 55% male
Number per group: Cemented: 41
Uncemented: 36
Observed adverse effects: "Radiological analysis demonstrated a marked difference between the two groups, with significantly more ($p < 0.001$, Mann-Whitney U test) radiolucency seen beneath the tibial trays in the cemented group. Radiolucency beneath the tibial component was not seen at final follow-up in the [tantalum metal tibial] uncemented group." Radiolucent lines beneath the tibial components may indicated separation and mechanical loosening."
The methods section reported collecting information on complications but did not specifically report any complications in the results section.
Timing of adverse effects: NR
Factors that predict response: Separation and loosening was not seen in uncemented components.

Source Citation: Zhang et al. 2020[1]

Study Design: Systematic review
Device or Material: Cement-augmented pedicle screws
Contract Duration: NR
Dose: NR
Frequency/Duration: NR
Response:

- Screw loosening
- Screw migration

Patient characteristics (gender, mean age): 20 studies (1,654 patients) with only 2 studies being prospective. Patient had vertebral fractures or degenerative spinal disease.
Number per group: NR
Observed adverse effects: "The pooled risk of screw related complications like screw loosening was 2.0% (0.2%-4.9%), screw breakage was 0.6% (0%-2.0%) and screw migration was 0.2% (0%-1.2%)."
Timing of adverse effects: NR
Factors that predict response: Degree of osteoporosis affects screw loosening but effect on bone cement is unknown.

Source Citation: McGuinness et al. 2019[13]

Study Design: Systematic review
Device or Material: Antibiotic-impregnated beads
Contract Duration: NR
Dose: NR
Frequency/Duration: NR

Response:
- Allergies
- Mechanical complications

Patient characteristics (gender, mean age): Used mostly for osteomyelitis and orthopedic prosthetic infections. The SR included 275 studies with 208 articles published on PMMA beads.
Number per group: NR
Observed adverse effects: "The majority of the reports we identified are case studies regarding rare events. These include allergies to components and red man syndrome from vancomycin beads. Mechanical complications have arisen with PMMA bead chains including damage to a bowel or veins in close proximity to the chain and inability to reduce a hip dislocation secondary to bead migration into the acetabulum. … There have also been reports of increased antibiotic resistance in organisms grown off of PMMA beads which were retained for an extended period of time."
Timing of adverse effects: NR
Factors that predict response: Allowing beads to remain for long periods rather than prompt removal

Source Citation: Sultan et al. 2019[14]
Study Design: Systematic review
Device or Material: Antibiotic-loaded bone cement
Contract Duration: NR
Dose: NR
Frequency/Duration: Single administration
Response:
- Toxicity

Patient characteristics (gender, mean age): Studies were included if patients received antibiotic-loaded bone cement in primary hip and knee arthroplasty with a minimum 2 year follow-up and the study reported complications related to bone cement. Information on age, gender and other patient characteristics were not reported.
Number per group: 24 studies, patients numbers were reported only for 7 studies of primary joint replacement (n = 88,258)
Observed adverse effects: The authors mentioned possible systemic and local toxicity of the antibiotics in the bone cement but did not report any concern with bone cement toxicity. The results section had no mention of bone cement toxicity. Systemic and local effects of antibiotics were unclear.
Timing of adverse effects:

Source Citation: Kammerlander et al. 2018[16]
Study Design: Randomized controlled trial
Device or Material: With and without cement augmented proximal femoral nail antirotation
Contract Duration: 12 months
Dose: TRAUMACEM V+ cement (DePuy Synthes, Oberdorf, Switzerland)
Frequency/Duration: Single administration
Response:
- Hypersensitivity or allergy
- Thromboembolism
- Local soft tissue reactions

Patient characteristics (gender, mean age): Closed trochanteric fracture (AO Type 31 A2–A3) due to a low energy trauma.
Augmented: 83% female, mean age 86.1 years
Nonaugmented: 84% female, mean age 85.6 years
Number per group: Augmented: n = 105
Nonaugmented: n = 118
Observed adverse effects: "For the safety population (n = 222), 41 patients (47%) in the proximal femoral nail antirotation augmentation group and 68 patients (50%) in the proximal femoral nail antirotation group had at least 1 reported complication (p = 0.681) during the study."
Augmented group: 0 hypersensitivity or allergy, 4 (5%) thromboembolic complications
Nonaugmented group: 1 hypersensitivity or allergy, 1 (1%) thromboembolic complications.

The authors noted that "No complications like hypersensitivity or local soft tissue reactions related to cement application were reported."

Timing of adverse effects: During 12-month follow-up

Factors that predict response: NR

Source Citation: van Hamersveld et al. 2017[17]

Study Design: Randomized controlled trial

Device or Material: Cemented or peri-apatite hydroxyapatite coating total knee arthroplasty

Contract Duration: 5 years

Dose: NR

Frequency/Duration: Single administration

Response:

- Deep vein thrombosis
- Implant migration

Patient characteristics (gender, mean age): Cemented: 43% female, 65.7 years

Uncemented: 63% female, 66.8 years

Number per group: Cemented: n = 30

Uncemented: n = 30

Observed adverse effects: "One cemented [total knee arthroplasty] was revised after three years due to ligament instability. No other revisions were performed. One patient in the cemented group had a deep vein thrombosis during hospital admission. One patient in the PA-coated group suffered a myocardial infarction ten months after discharge but continued to participate in the study. Patients with components showing high migration are clinically still asymptomatic; no revisions due to aseptic loosening have been performed yet." No other adverse events or complications were noted in the adverse events section of the report.

Timing of adverse effects:

Source Citation: Wallace and Henshaw 2014[19]

Study Design: Retro comparison study

Device or Material: Bone cement compared to bone graft material

Contract Duration: PMMA: 2 to 11.5 years

Bone graft: 2 to 8 years

Dose: NR

Frequency/Duration: Single administration

Response:

- Fractures
- Growth deformity
- Pain

Patient characteristics (gender, mean age): Pediatric patients (younger than 16 years) were treated for benign locally aggressive and/or low grade malignant bone lesions.

PMMA group: 12.4 years;

Bone graft group: 11.3 years

Number per group: PMMA group: n = 17

Bone graft group: n = 19

Observed adverse effects: Fractures: none in the cement group, 3 in the bone graft group.

Reoperation: "5 patients required a second operation in the PMMA group (rate 29.4%), compared to 6 reoperations in the grafted group (rate 31.6%)."

Growth: 1 patient in the PMMA series required femoral shortening for a longitudinal growth deformity, and 1 patient who received bone graft required a physeal arrest procedure for an angular growth deformity."

Pain after surgery: only 2 cement patients required daily medication for postoperative pain and 3 bone graft patients complained of long-term pain.

There were no statistically significant differences between the PMMA and bone graft group in terms of patient age, length of follow-up, or complications rates."

Timing of adverse effects: NR

Factors that predict response: "PMMA cement has the mechanical advantage of providing immediate structural support to the bone, absorbing stress, and protecting areas that are at risk for postoperative fracture, including the metaphyseal-diaphyseal junction and subchondral regions of the epiphysis where many tumors invade. … The use of PMMA in our case series was associated with complication rates of adjacent joint arthrosis and growth-related deformity that are comparable to those observed within our bone graft control series."

Source Citation: Lass et al. 2013[18]

Study Design: Nonrandomized controlled study
Device or Material: Total knee arthroplasty (TKA): titanium-coated cementless implants compared with hybrid TKA implants with a cemented tibial and a cementless femoral component
Contract Duration: Minimum 5 years
Dose: NR
Frequency/Duration: Single administration
Response:

- Postoperative complications: poor initial fixation, aseptic loosening indicated by radiolucent lines, and osteolysis

Patient characteristics (gender, mean age): Cemented: 14 male, 46 female; 68.1 years
Uncemented: 25 male, 35 female; 65.7 years
Number per group: Cemented: n = 60
Uncemented: n = 60
90 operated knees in 81 patients were analyzed for a minimum of 5 years postoperatively." 43 cementless, 47 hybrid.
Observed adverse effects: "The current study showed no significant difference between cementless and hybrid cemented TKAs over the 5-year follow-up in terms of clinical and functional results and postoperative complications.
"Radiolucent lines of less than 1 mm were found in 10 (23.2%) patients in the cementless group and in 14 (29.7%) patients in the hybrid cemented group. … In the current study, the authors noted a significant difference in mean anteroposterior tibial scores [tibia radiolucent line scores] for the hybrid cemented and cementless groups of 1.83 and 0.43, respectively, (P<0.001) and in mean lateral tibial scores for the hybrid cemented and cementless groups of 0.35 and 0.07, respectively (P=0.010)."
Timing of adverse effects: Mean 6-year follow-up
Factors that predict response: "The significantly smaller number of radiolucent lines in the cementless group in the mid-term results is an indicator of primary stability with benefits for the fixation durability of TKA in the long term."

Systemic Response/Toxicity

Source Citation: Zhang et al. 2020[1]

Study Design: Systematic review
Device or Material: Cement-augmented pedicle screws
Contract Duration: NR
Dose: NR
Frequency/Duration: NR
Response:

- Cement leakage
- Pulmonary embolism

Patient characteristics (gender, mean age): 20 studies (1,654 patients) with only 2 studies being prospective. Patient had vertebral fractures or degenerative spinal disease.
Number per group: NR
Observed adverse effects: "On the pooling of data from 1,277 patients, we found the risk of all cement leakage to be 21.8% (95% CI: 6%-43.1%, I2= 98.38%). … Pooled analysis of data from 1,654 patients indicated the risk of symptomatic cement leakage to be 1.2% (95% CI: 0.6%-1.9%, I2= 0%)… We found the risk of pulmonary embolism with [cement-augmented pedicle screws] to be 3.0% (95% CI: 0.5%-6.8%, I2= 85.43%) after pooling data from 11 studies with 1,158 patients. On the other hand, the risk of symptomatic

pulmonary was found to be 0.8% (95% CI: 0.2%-1.5%, I2= 0%) after pooling data from the same 11 studies."

Timing of adverse effects: NR

Factors that predict response: NR

NR = not reported; PA = peri-apatite; PMMA = polymethyl methacrylate

Table 9: Orthopedic components - Health Effect (In Vivo) Human Studies

Local Response/Toxicity

Source Citation: Li et al. 2019[20]

Study Design: Nonrandomized comparisons
Device or Material: Hip replacement with and without spacer
Contract Duration: Mean duration 24.2 months
Dose: Cement spacer group, 8 g vancomycin (Lilly, Indianapolis, IN, USA) mixed with 80 g of bone cement (Refobacin; Zimmer Biomet, Warsaw, IN, USA)
Frequency/Duration: Single administration
Response:
- Infection

Patient characteristics (gender, mean age): 8 men and 5 women, mean age 59.3 ± 4.3 years
Number per group: 13; 4 resection of head and neck only, 9 resection plus antibiotic bone cement
Observed adverse effects: "No cases had an infection recurrence or emerging infection surrounding the prosthesis, and no cases had prosthesis loosening, a dislocation, or a fracture around the prosthesis during the follow-up periods."
Timing of adverse effects: NR
Factors that predict response: "The comparison of the results from the follow-up in patients undergoing different surgical procedures showed that the application of an antibiotic cement spacer in addition to a head and neck resection could better control the infection."

Source Citation: Staats et al. 2017[2]

Study Design: Nonrandomized comparison study
Device or Material: Antibiotic- loaded spacer (ALS)
Contract Duration: Mean follow-up was 46 months (range 12–139 months)
Dose: Antibiotic bone cement containing 0.5 g gentamicin and 2 g vancomycin per 40 g bone cement (COPAL G+V 40, Heraeus, Wehrheim, Germany)
Frequency/Duration: Single administration
Response:
- Reinfection

Patient characteristics (gender, mean age): ALS: 67 years, 40% female. No ALS: 61 years, 52.4% female.
Number per group: 46 2-stage hip revision surgery. 25 with ALS, 21 no ALS.
Observed adverse effects: "Kaplan–Meier analysis revealed a revision-free survival in the non-ALS group of 76.1% (n = 16) at 12 months, 71.4% (n = 15) at 24 months and a long-term revision-free survival rate of 66.6% (n = 14). The group with ALS implantation showed a revision-free survival rate of 100% (n = 25) at 12 months, 100% (n = 25) at 24 months and a long-term revision-free survival rate of 92% (n = 23)." No other complications were reported.
Timing of adverse effects: NR
Factors that predict response: Presence of ALS

Source Citation: Verhelst et al. 2011[21]

Study Design: Retrospective nonrandomized comparison study
Device or Material: Orthopedic spacer
Contract Duration: Mean follow-up of 46.4 months
Dose: Refobacin R bone cement (PMMA) loaded with 0.5 g gentamycin antibiotic
Frequency/Duration: Single administration
Response:
- Reinfection

Patient characteristics (gender, mean age): 11 female, 10 male, mean age of 66.7 years (range 33.6-85.1 years)
Number per group: 10 received spacer, 11 did not receive spacer

Observed adverse effects: Control of infection did not differ significantly between the groups. No improved outcomes demonstrated with the use of cement spacer. 2 patients had low grade infections, all others did not show signs of infection.
Timing of adverse effects: Mean follow-up of 22 months
Factors that predict response: NR

Table 10: Ocular Implants/IOL- Health Effect (In Vivo) Human Studies

Local Response/Toxicity

Source Citation: Bautista-Llamas et al. (2019)[22]

Study Design: Systematic review
Device or Material: Intacs, Ferrara, or Keraring ICRS, all made of PMMA
Contract Duration: Mean follow-up 56.9 weeks
Dose: NR
Frequency/Duration: Single administration
Response:

- Corneal thinning
- Corneal melting
- Migration
- Ring extrusion
- Keratitis
- ICRS explantation

Patient characteristics (gender, mean age): 1,213 male, 733 female, mean age 33.45 years.
Number per group: Included 39 studies with 1,946 patients (2,590 eyes). Intacs: 448 eyes, Ferrara or Keraring: 1,804 eyes, Intacs and Keraring: NR.
Observed adverse effects: Analysis of combined incidents of postoperative complications was not performed. "Postoperative complications were described in most studies: migration, ring extrusion, corneal thinning, corneal melting, and type of infective keratitis". "According to ICRS type reviewed, Ferrara and Keraring ICRS reported a 1% explantation rate, and Intacs reported a 19% explantation rate." "Most Intacs were explanted for low quality vision reasons."
Timing of adverse effects: Follow-up range: 2 to 240 weeks
Factors that predict response: "Keraring and Ferrara Ring are more effective in the treatment of keratoconus compared with Intacs. "This notion is justified by the larger diameter of the Intacs, which induces minimal corneal central flattening", which may increase halos and glare.
SR did not examine non-PMMA ICRSs so complications could be related to ICRS surgery. The authors noted that "trauma to the incision and tunnel results in increased keratocyte apoptosis, major tissue degradation, and a subsequently increased number of complications, such as corneal melting."

Source Citation: de la Paz et al. 2019[3]

Study Design: Retrospective nonrandomized comparison study
Device or Material: Boston type I KPro compared with biological KPros (osteo-odonto-KPro (OOKP) and tibial bone KPro)
Contract Duration: Median follow-up: OOKP 16.8 years, tibial bone KPro 4.2 years, Boston KPro 3.4 years
Dose: NR
Frequency/Duration: Single administration
Response:

- Endophthalmitis
- Retinal detachment
- RPM formation
- Glaucoma
- Vitreous hemorrhage
- Buccal mucosa necrosis
- KPro exchange

Patient characteristics (gender, mean age): All patients had chemical injuries or autoimmune diseases affecting the eye. OOKP: 20 male eyes and 3 female eyes, median age 38 years, range 17 to 55 years. Tibial bone KPro:

14 male eyes and 8 female eyes, median age 50 years, range 24 to 86 years. Boston KPro: 20 male eyes and 5 female eyes, median age 49 years, range 20 to 84.
Number per group: OOKP: 23 eyes, tibial bone KPro: 22 eyes, Boston KPro: 25 eyes
Observed adverse effects: In patients with chemical injuries or autoimmune diseases affecting the eye, there was a higher incidence of RPM formation in the Boston KPro group compared to OOKP and tibial bone KPro groups. "Glaucoma also had a higher incidence in the Boston KPro group in chemical injury cases. There were 5 cases (chemical injury = 3, autoimmune = 2) that underwent KPro exchange in the Boston KPro group: three cases for corneal melting and extrusion, one case for retroprosthetic membrane and extrusion, and one case due to fungal endophthalmitis." There were no KPro exchanges in the OOKP or tibial bone KPro groups during the study period.
Timing of adverse effects: Median follow-up range: OOKP 0.1 to 30.3 years, Tibia bone KPro 0.1 to 13.1 years, Boston KPro 0.1 to 8.8 years.
Factors that predict response: "In autoimmune diseases the response of the ocular tissue to any type of major surgery is more aggressive, with an increased inflammatory response, which, in most cases, may even need systemic immunosuppression. Moreover, subclinical relapses and unexpected recurrences of the a utoimmune process can in addition affect the final outcome of the KPro." With chemical injury and autoimmune diseases, there was a tendency for better long term anatomical and functional results with Tibial bone KPro followed by OOKP and Boston KPro Type 1. However, these results were not statistically significant.

Source Citation: Izquierdo et al. 2019[23]
Study Design: Systematic review
Device or Material: ICR versus ICR + corneal cross-linking (CXL)
All ICRs are made of PMMA
Contract Duration: Follow-up: 12 months
Dose: NR
Frequency/Duration: Single administration
Response:
- Corneal melting
- Decentration
- Eye edema
- Migration
- Extrusion
- Epithelial defect
- White deposit
- Keratitis
- Perforation
- Neovascularization
- Recurrent epithelial erosion
- Break of segments

Patient characteristics (gender, mean age): Adult patients with keratoconus, treated with Keraring, Myoring, Ferrara ring, Intacs, or Intacs SK
Number per group: ICR: 991 eyes, ICR + CXL: 334 eyes
Observed adverse effects: "The primary complications in the ICR group were white deposits (57 [5.75%]), epithelial defects (56 [5.65%]), extrusion (21 [2.11%]), decentration (14 [1.41%]), segment migration (6 [0.6%]), and … [corneal melting (4 [0.4%])]. In the ICR and CXL group, the main complications were edema (17 [5.08%]), extrusion (2 [0.59%]), perforation (2 [0.59%]), and corneal melting (1 [0.29%])."
Timing of adverse effects: Up to 12 months
Factors that predict response: "Intraoperative complications are mainly linked to the construction of the tunnel in manual techniques. The most frequent are decentration of the segments, inadequate depth of the tunnel, and asymmetry of the segments."

Source Citation: Priddy et al. 2019[24]
Study Design: Systematic review

Device or Material: Boston type I KPro
Contract Duration: Mean follow-up: 24 to 66 months
Dose: NR
Frequency/Duration: Single administration
Response:

- Keratolysis (corneal melt/thinning/infiltrate/necrosis, stromal necrosis, keratitis, KPro
- leak, and epithelial defect)
- RPM formation
- Endophthalmitis
- Glaucoma
- Hypotony/Phthisis
- Sterile vitritis/Uveitis
- Vitreoretinal complications (retinal/choroidal detachment, choroidal/vitreous hemorrhage, cystoid macular edema, choroidal effusion, and epiretinal/preretinal membrane)
- Wound dehiscence (Boston KPro dehisced uveal prolapse/ruptured due to trauma and graft extrusion)

Patient characteristics (gender, mean age): Median 38% female, mean age range 35.4 to 71.3 years
Number per group: 1,482 patients (1,619 eyes) in 30 studies
Observed adverse effects: The combined incidence of RPM across 29 studies was 36.6% (95% CI, 30.5% to 42.6%). The combined incidence of glaucoma, vitreoretinal complications, and keratolysis across 19 studies was 39.3% for glaucoma (95% CI 28.8%–49.7%), 27.5% for vitreoretinal complications (95% CI 20.9%–34.2%), and 14.5% for keratolysis (95% CI 11.3%–17.6%). The combined incidence of endophthalmitis across 11 studies was 6.1% (95% CI 3.8%–8.4%). The combined incidence of sterile vitritis/uveitis and hypotony/phthisis across 9 studies was 8.9% for sterile vitritis/uveitis (95% CI 5.6%–12.1%) and 7.6% for hypotony/phthisis (95% CI 4%–11.6%). The combined incidence of wound dehiscence across 5 studies was 9.8% (95% CI 4%–15.5%).
Timing of adverse effects: 2 to 5 years
Factors that predict response: "High-quality, long-term studies on Boston type 1 KPro outcomes are needed, especially as complications and outcomes worsen with increased follow-up time. Our research further highlights the lack of evidence for Boston type 1 KPro long-term outcomes. Future studies in this area could significantly impact which patients' Boston type 1 KPros are deemed suitable for."

Source Citation: Shanbhag et al. 2018[25]
Study Design: Systematic review
Device or Material: Boston type I KPro
Contract Duration: Mean follow-up: 24.99 ± 14 months
Dose: NR
Frequency/Duration: Single administration
Response:

- Corneal necrosis/melt/thinning
- RPM formation
- Extrusion
- Epithelial defect
- Glaucoma
- Keratitis
- Hypotony
- Retinal detachment
- Cystoid macular edema/epiretinal membrane
- Endophthalmitis
- Sterile vitritis
- Choroidal effusion

Patient characteristics (gender, mean age): All 100 patients had corneal blindness secondary to severe chemical ocular injury. 47 patients had chemical injuries affecting both eyes. Other patient characteristics NR.
Number per group: 100 patients (102 eyes)

Observed adverse effects: Corneal necrosis/melt/thinning was the highest incident postoperative complication, occurring in 23/102 eyes (22.6%). RPM formation occurred in 21/102 eyes (20.6%), glaucoma progressed in 14/102 eyes (13.7%), Boston Type 1 KPro extrusion occurred in 12/102 eyes (11.8%), retinal detachment occurred in 8/102 eyes (7.8%), and epithelial defect occurred in 6/102 eyes (5.9%). Less frequent postoperative complications included hypotony, keratitis, and cystoid macular edema/epiretinal membrane, each occurring in 5/102 eyes (4.9%). Sterile vitritis and choroidal effusion each occurred in 3/102 eyes (3%) and endophthalmitis occurred in 2/102 eyes (1.96%).

Timing of adverse effects: Mean follow-up range: 5 to 98 months

Factors that predict response: NR

Source Citation: Talati et al. 2018[4]

Study Design: Retrospective matched nonrandomized comparison study

Device or Material: Boston type 1 KPro using titanium or PMMA backplate

Contract Duration: Mean follow-up: titanium 28.1 ± 8.9 months, PMMA 53.6 ± 24.3 months

Dose: NR

Frequency/Duration: Single administration

Response:

- RPM formation
- Avascular fibrous tissue membrane representing host stromal cell down growth over the device

Patient characteristics (gender, mean age): Titanium: 10 male and 10 female, median age 60.2, range 31 to 85 years
PMMA: 5 males and 15 females, median age 67.4 years, range 27 to 82 years

Number per group: 40 patients, 20 in each matched group

Observed adverse effects: "At 12 months postoperatively, 7 eyes with titanium and 6 eyes with PMMA backplates developed a visually significant RPM. By the end of the study, a total of 11 eyes with titanium and 9 eyes with PMMA KPros developed a visually significant RPM. There was no statistically significant difference between both groups."

Timing of adverse effects: NR

Factors that predict response: "Although this study is not powered to completely exclude an effect of titanium in RPM formation, our results support the findings of Rudnisky et al and suggest that host factors play a more critical role than the backplate material in the pathophysiology of the RPM."

Source Citation: Naik et al. 2017[29]

Study Design: Prospective nonrandomized comparison study

Device or Material: Flexible, hydrophobic acrylic PCIOL versus rigid PMMA PCIOL. Both groups with or without a CTR

Contract Duration: Follow-up: 35 days

Dose: NR

Frequency/Duration: Single administration

Response:

- Eye edema
- Hyphema
- Inflammation
- Intraocular pressure elevation
- Striate keratopathy

Patient characteristics (gender, mean age): Acrylic PCIOL: 38 males, 12 females. PMMA PCIOL: 38 males, 12 females. Mean age for both groups: 67.95±6.77 years

Number per group: Acrylic PCIOL: 38 male eyes, 12 female eyes, 1 CTR in 1 eye: gender NR. PMMA PCIOL: 38 male eyes, 12 female eyes, 5 CTRs in 5 eyes: gender NR.

Observed adverse effects: There was no statistically significant difference in postoperative complications between groups. Edema was the highest incident postoperative complication in both groups, occurring in 2/50 eyes (4%) of the acrylic PCIOL group and 4/50 eyes (8%) of the PMMA PCIOL group. In the acrylic PCIOL group, inflammation, striate keratopathy, and increased intraocular pressure each occurred in 1/50 eyes (2%). In the PMMA PCIOL group, striate keratopathy occurred in 3/50 eyes (6%) whereas inflammation, hyphema, and increased intraocular pressure each occurred in 1/50 eyes (2%).

Timing of adverse effects: Follow-up range: 7 to 35 days

Factors that predict response: NR

Source Citation: Ahmad et al. 2016[26]

Study Design: Systematic review
Device or Material: Boston KPro vs. repeat penetrating keratoplasty (PK)
Contract Duration: Up to 5 years
Dose: NR
Frequency/Duration: Single administration
Response:

- Glaucoma
- Infection

Patient characteristics (gender, mean age): NR for PK studies.
KPro: mean 63.3 years, 57% female
Number per group: PK studies of glaucoma n = 542. PK studies of infection n = 362. KPro n = 98 (104 eyes).
Observed adverse effects: PK: "Eight studies reported the rate of glaucoma after repeat PK surgery. The proportion of patients having glaucoma after repeat PK was 25% (95% CI 10% to 44%; I2 = 95.4%). "The average follow-up for these studies was 31 months (range, 9 to 72 months). … Three studies reported the infectious keratitis rate after repeat PK surgery, and their mean follow-up was 47 months (range, 25 to 72 months). The proportion of patients having infectious keratitis after repeat PK was 18% (95% CI, 9% to 30%; I2 = 83.4%)"
KPro: At year 2, 28.8% of patients experienced an elevation in IOP and 7.9% required glaucoma surgery. … "At year 5, 30.7% of patients experienced an elevation in IOP and 13.5% required glaucoma surgery. … The rate of infectious keratitis and endophthalmitis at 5 years was 2.9% and 10.3%, respectively, for all patients."
Timing of adverse effects: NR
Factors that predict response: "Although KPro surgery was once considered a last-resort procedure owing to its side effect profile of glaucoma and infection, new designs and better postoperative management have led to more encouraging outcomes."

Source Citation: Li et al. 2016[27]

Study Design: Systematic review
Device or Material: Modified CTRs— Cionni modified CTR 1L, Cionni modified CTR 2L, Cionni modified CTR 2C, or Malyugin modified CTR
Contract Duration: Mean follow-up: 23.8 months
Dose: NR
Frequency/Duration: Single administration
Response:

- PCO
- Cystoid macular edema
- IOP elevation
- Glaucoma
- Traumatic corectopia
- Uveitis

Patient characteristics (gender, mean age): Adult and pediatric patients who had surgical indications for modified CTR use during cataract surgery. Mean age 28.3 years.
Number per group: 10 studies with 229 adult eyes, 91 pediatric eyes
Observed adverse effects: "The overall rate of postoperative PCO was 41.1% (118/287). The rate in adult eyes was 25.6% (50/196) and in pediatric eyes, 74.7% (68/91). Other postoperative complications reported in the studies were intraocular pressure (IOP) spike (18 cases), suture breakage requiring resuturing (11 cases), chronic uveitis (5 cases), cystoid macular edema (2 cases), need for glaucoma filtration surgery (2 cases), and traumatic corectopia (2 cases)."
Timing of adverse effects: Mean follow-up range: 12.9 to 48.0 months
Factors that predict response: NR

Source Citation: Al Arfaj et al. 2015[5]

Study Design: Systematic review
Device or Material: Boston type 1 and type 2 KPro
Contract Duration: Follow-up range: 1 week to 85 months
Dose: NR
Frequency/Duration: Single administration
Response:

- Corneal melt
- RPM formation
- Endophthalmitis
- Glaucoma
- IOP elevation
- Retinal detachment

Patient characteristics (gender, mean age): NR
Number per group: Boston Type 1 KPro: approximately 1,400 eyes, Boston Type 2 KPro: 11 eyes. RPM: 10 studies and 657 eyes
Observed adverse effects: Combined incidents of postoperative complications were reported. "RPM is one of the most common complications (affecting 12–67% of eyes) after B-KPro. Literature review revealed endophthalmitis prevalence rate of 0-13% [and] retinal detachment…in 5–19% of the eyes" implanted with Boston KPro. "The incidence of corneal melt as reported in the literature is also high (1.5–17%). While elevated intraocular pressure (IOP) (14–100% eyes) and glaucoma (2–43% eyes) were a common complication, it did not seem to affect the retention rates."
Timing of adverse effects: Follow-up range: 1 week to 85 months
Factors that predict response: "The expected outcomes seemed to be influenced by the primary indications. Apparently, best results were observed in non-cicatrizing conditions and preoperative conditions such as autoimmune diseases, chemical injury, LSCD [limbal stem cell deficiency], deep corneal vascularization were found to be associated with studies reporting lower retention rates."

Source Citation: Lee et al. 2015[6]

Study Design: Systematic review
Device or Material: Boston type I KPro
Contract Duration: Mean follow-up range – 2.0 to 47.0 months
Dose: NR
Frequency/Duration: Single administration
Response:

- Corneal melt
- RPM formation
- Glaucoma
- Keratitis
- Endophthalmitis
- Hypotony/Choroidal effusion
- Retinal detachment
- Scleritis
- Sterile vitritis
- Suprachoroidal hemorrhage

Patient characteristics (gender, mean age): NR
Number per group: 2,176 eyes
Observed adverse effects: "The most common complication after BI-KPro implantation was RPM formation. The occurrence of RPM ranged from 1% to 65% (mean±SD, 30.0±19.0%) in the 13 articles that reported this complication. Follow-up ranged from 6 to 47 months (mean±SD, 18.5±11.5 months). Glaucoma after KPro implantation occurred in 2.4% to 64.0% of eyes (mean±SD, 27.5±18.1%), with follow-up ranging from 6 to 47 months (mean±SD, 18.6±11.0 months). Corneal melting (keratolysis) was described in 12 publications, with a range of 2.4% to 30.4% (mean±SD, 13.0±9.8%) and an average follow-up of 6 to 47 months (mean±SD, 21.3±12.2 months). Infectious keratitis was listed as a complication in 5 of the 22 articles. The

incidence ranged from 0% to 17.8% (mean±SD, 12.7±4.4%), with a follow-up ranging from 14.2 to 26.2 months (mean±SD, 20.0±4.6 months). [e]ndophthalmitis was the most common posterior segment complication after KPro implantation. Fifteen publications reported whether it developed, with a range from 0% to 12.5% (mean±SD, 4.6±4.6%) and follow-up ranging from 8.5 to 47 months (mean±SD, 21.7±11.5 months)." Sterile vitritis "was reported in 10 of 13 publications that covered this complication. The range of vitritis was 0% to 14.5% (mean±SD, 5.6±4.7%), with followup ranging from 8.5 to 47 months (mean±SD, 18.8±10.0 months)." "The incidence [of scleritis] ranged from 0% to 5.4% (mean±SD, 0.8±1.9%), with a follow-up ranging from 6 to 22 months (mean±SD, 14.9±5.4 months)." Of 16 studies, retinal detachment and hypotony/choroidal effusion were reported in 13 studies, whereas suprachoroidal hemorrhage was reported in 14 studies. The incidence of retinal detachment ranged from 0% to 19.0%. The incidence of hypotony/choroidal effusion ranged from 0% to 16.9%. The incidence of suprachoroidal hemorrhage ranged from 0% to 6.0%.

Timing of adverse effects: Mean follow-up range: 2.0 to 47.0 months

Factors that predict response: "The potential for complications increases with time after BI-KPro surgery and with eyes that are predisposed to inflammatory effects around the back plate of the KPro device. As follow-up times increased, a pattern of lower device retention was seen. Accordingly, all patients with the BI-KPro device should be followed up as glaucoma suspects, given the high risk of elevated IOP and associated visual field loss, optic nerve damage, or both."

Source Citation: Hennig et al. 2014[9]

Study Design: RCT

Device or Material: Flexible, hydrophilic acrylic IOL (IOCare, RYCF-6) versus rigid PMMA IOL (IOCare, PH5)

Contract Duration: Median follow-up: acrylic IOL, 395 days, PMMA IOL, 394 days

Dose: NR

Frequency/Duration: Single administration

Response:

- PCO
- Eye edema
- IOP elevation
- Uveitis

Patient characteristics (gender, mean age): All patients had phacoemulsification followed by IOL implantation. Acrylic IOL: 247 males, 342 females, mean age 57.4±8.7 years. Rigid PMMA IOL: 244 males, 367 females, mean age 56.9±8.8 years.

Number per group: Acrylic IOL: 247 male eyes, 342 female eyes. PMMA IOL: 244 male eyes, 367 female eyes.

Observed adverse effects: At 1-year follow-up, increased IOP nor uveitis were noted in either group. One case of corneal edema was reported in the acrylic IOL group. "PCO was significantly more common in the rigid PMMA IOL group." At 1-year follow-up, there were 99 new PCO cases in the acrylic IOL group and 164 new PCO cases in the PMMA IOL group ($p < 0.001$).

Timing of adverse effects: Median follow-up range: 135 to 706 days

Factors that predict response: "The increased risk of capsule opacification [PCO] in rigid PMMA IOLs can be reduced by a square edge design of the optic. Only the foldable IOLs used in this trial had a square edge design."

Source Citation: Leung et al. 2014[28]

Study Design: Systematic review

Device or Material: Hydrophobic acrylic IOL, hydrophilic acrylic IOL, silicone IOL, and PMMA IOL with or without heparin-surface modification (HSM)

Contract Duration: Follow-up range: <1 month to 24 months

Dose: NR

Frequency/Duration: Single administration

Response:

- Inflammation
- PCO
- Posterior synechiae
- Eye edema

Patient characteristics (gender, mean age): 216 patients with uveitis and surgical indications for IOL use during cataract surgery. 85 males, 129 females, 2: gender NR. Other patient characteristics: NR.
Number per group: Hydrophobic acrylic: 108 eyes, hydrophilic acrylic: 60 eyes, silicone: 44 eyes, PMMA: 42 eyes, PMMA+HSM: 38 eyes.
Observed adverse effects: Analysis of combined incidences of postoperative complications was not performed. "There were no statistically significant differences in outcomes among eyes of people randomized to receive [PMMA+HSM] IOLs when compared with fellow eyes receiving PMMA IOLs. 13 (42%) eyes randomized to hydrophobic versus two (8%) eyes randomized to hydrophilic acrylic IOLs developed 1+ or greater giant cell deposits on IOL (RR 6.50, 95% 1.60 to 26.36). Fewer eyes with hydrophobic acrylic IOLs developed posterior synechiae of any severity or experienced postoperative inflammation compared with eye with silicone IOLs. Eyes randomized to hydrophobic acrylic IOLs were reported to have been less likely to develop PCO six months postsurgery compared with eyes randomized to silicone IOLs (data not reported); however, this difference was less certain after one year (RR 0.74, 95% CI 0.41 to 1.37)."
Timing of adverse effects: Follow-up range: <1 month to 24 months
Factors that predict response: "There is ethnic/geographic variation in the etiology of uveitis, but the limited results we have from the largest of the four studies suggest that the chance of improved visual outcome is higher and the risk of complication is lower when using hydrophobic acrylic rather than silicone lenses.
"These studies, including a combined total of 16 participants with uveitis, were insufficiently powered to detect differences in outcomes among eyes of people with uveitis randomized to receive HSM PMMA IOLs when compared with fellow eyes receiving unmodified PMMA IOLs."

Source Citation: Bayyoud et al. 2013[30]
Study Design: Retrospective nonrandomized comparison
Device or Material: With and without CTR
Contract Duration: Mean follow-up: CTR 24 months, without CTR 28 months
Dose: NR
Frequency/Duration: Single administration
Response:
- Cystoid macular edema
- Secondary cataract
- IOP elevation

Patient characteristics (gender, mean age): Cataract surgery with and without CTR in a group of patients with retinitis pigmentosa.
Mean age at surgery 53 years, 29 male, 23 female
Number per group: CTR: 26 eyes, without CTR: 26 eyes,
Observed adverse effects: CTR: 10 eyes (38%) secondary cataracts, and 1 (4%) with cystoid macular edema and elevated intraocular pressure.
Without CTR: 13 eyes (50%) secondary cataracts, 4 eyes (15%) with intraocular pressure elevation, and 2 eyes (8%) with capsular contraction syndrome and cystoid macular edema. "Surgery with capsular tension ring implantation resulted in fewer long-term postoperative complications including secondary cataract and capsular contraction syndrome."
Timing of adverse effects: NR
Factors that predict response: NR

Source Citation: Sanghi et al. 2011[7]
Study Design: Prospective nonrandomized comparison study
Device or Material: Rigid heparin surface-modified PMMA IOL and foldable acrylic IOL
Contract Duration: Follow-up: 1 to 5 years
Dose: NR
Frequency/Duration: Single administration
Response:
- Primary posterior capsulotomy plus anterior vitrectomy
- Mean reaction (degree of uveitis)
- Synechiae (adhesions formed between adjacent structures within the eye as a results of inflammation)

- PCO

Patient characteristics (gender, mean age): Mean age was 4.2 years at surgery, range 3 months to 11 years. 18 male, 8 female. A single-bolus dose of intravenous hydrocortisone (5 mg/kg of body weight) and d examethasone (0.1 mg/kg of body weight) was given as an adjunct after pediatric cataract surgery.
Number per group: 42 eyes of 26 patients. 19 rigid and 23 foldable.
Observed adverse effects: There was no difference in the inflammation and postoperative complications in children 3 years and younger vs. those older than 3 years and also rigid vs. foldable IOL implantation. Primary posterior capsulotomy plus anterior vitrectomy: rigid 68%, foldable 65%. Mean reaction: rigid 0.63, foldable 0.35. Synechiae: rigid 0%, foldable 8.7%. Posterior capsule opacification: rigid 31.6%, foldable 8.7%
Timing of adverse effects: NR
Factors that predict response: "The inflammatory reaction and postoperative complications are low even with rigid IOLs and a younger subset of patients (<3 years) who are prone to develop more inflammation. Heparin minimizes postoperative inflammation." "A single intravenous bolus of hydrocortisone and dexamethasone seems to be a promising method for minimizing postoperative inflammation and later complications of pediatric cataract surgery."

Source Citation: Todani et al. 2011[10]

Study Design: Retrospective nonrandomized comparison study
Device or Material: Boston type 1 KPro with titanium snap-on backplate, PMMA snap-on backplate, or PMMA screw-on backplate
Contract Duration: Follow-up: 6 months
Dose: NR
Frequency/Duration: Single administration
Response:

- RPM formation

Patient characteristics (gender, mean age): 42 males, 31 females, mean age 58.39 years, range 17 to 94 years
Number per group: 73 patients (78 eyes). Titanium: 23 eyes, Snap-on PMMA: 16 eyes, Screw-on PMMA: 39 eyes.
Observed adverse effects: At 6-months follow-up, the screw-on PMMA backplate group had the highest RPM incidence affecting 18/39 eyes (46.1%). At 6-months follow-up, the RPM incidence in the snap-on PMMA backplate group was 5/16 eyes (31.2%) and the RPM incidence in the snap-on titanium backplate group was 3/23 eyes (13.0%). There was no significant difference between RPM formation in PMMA snap-on and screw-on backplate groups (p = 0.309, Chi-square test). Combining the PMMA group results for analysis showed that PMMA backplates were "associated with significantly more RPM than titanium…(p=0.014, Chi-square test)."
Timing of adverse effects: Follow-up: 6 months
Factors that predict response: "A total of 145 such devices [with titanium snap-on backplates] have been implanted. The overall clinical impression has been favorable: it has been the unanimous opinion of all collaborators that titanium seems to cause less postoperative reaction than PMMA…Only three devices had to be replaced, all of which were implanted in autoimmune patients."

Systemic Response/Toxicity

Source Citation: Paschalis et al. 2019[31]

Study Design: Prospective nonrandomized comparison study
Device or Material: Boston type 1 KPro versus control group with no KPro
Contract Duration: Mean 5.3 ± 3.7 years from Kpro surgery
Dose: NR
Frequency/Duration: Single administration
Response: Blood plasma levels of soluble TNF-α, TNF receptors 1 (TNFR1) and 2 (TNFR2), and leptin (tissue necrosis factor)
Patient characteristics (gender, mean age): KPro group: 62 ±14, 8% female. Non-KPro group: 65 ± 8, 21% male.
Number per group: 65 total. Boston KPro = 31, no KPro = 34.
Observed adverse effects: "We detected elevated serum levels of TNF-α and TNFR2 in KPro patients compared to non Kpro patients. … The elevated blood levels of TNF-α and TNFR2 are found years after KPro surgery and

remained significant after adjustment for glaucoma, [intraocular pressure], BMI, gender, and race." TNF is an inflammatory cytokine.

Timing of adverse effects: NR

Factors that predict response: "TNF upregulation in KPro patients may be a result of ocular inflammation."

CI = confidence interval; CTR = capsular tension ring; CXL = corneal cross-linking; ICR = intrastromal corneal ring; ICRS = intracorneal ring segments; IOL = intraocular lens; IOP = intraocular pressure; KPro = keratoprosthesis; NR = not reported; PCIOL = posterior chamber intra-ocular lens; PCO = posterior capsule opacification; PMMA = polymethyl methacrylate; RPM = retroprosthetic membrane; SD = standard deviation; TNF = tissue necrosis factor; TNF-α = tissue necrosis factor alpha.

Table 11: Dermal Filler - Health Effect (In Vivo) Human Studies

Local Response/Toxicity

Source Citation: Tachamo et al. 2018[33]

Study Design: Systematic Review
Device or Material: PMMA cosmetic injection
Contract Duration: NR
Dose: NR
Frequency/Duration: NR
Response:
- Hypercalcemia associated with foreign body granulomatous reaction

Patient characteristics (gender, mean age): 23 eligible patients in 20 articles, 49.83 ± 14.70 years, 78% female
Number per group: 7 of 23 were injected with PMMA
Observed adverse effects: Renal failure in the worse cases (82%). Number associated with PMMA was NR.
Timing of adverse effects: Onset from initial injection averaged 7.96 years, range months to 28 years, data not specific for PMMA.
Factors that predict response: NR

Source Citation: Karnik et al. 2014 [32]

Study Design: RCT
Device or Material: PMMA cosmetic injection, PMMA compared to saline injection
Contract Duration: 6 months Dose: 0.11 mL of PMMA for each scar; No more than 5.8 mL PMMA total
Frequency/Duration: Two administrations
Response:
- Injection site tenderness
- Swelling
- Influenza
- Nasopharyngitis

Patient characteristics (gender, mean age): 61% female, 39% male, 44 years
Number per group: 96 PMMA, 49 saline
Observed adverse effects: Minor, reversible AEs including swelling and tenderness
Timing of adverse effects: On average, the majority of AEs manifested and resolved within 2 days
Factors that predict response: NR

Source Citation: Paulucci BP 2020 [11]

Study Design: Systematic Review
Device or Material: PMMA cosmetic injection
Contract Duration: Average of 12 months
Dose: Average injected volume was 2.8 ml
Frequency/Duration: Multiple administrations
Response:
- Granuloma
- Persistent swelling
- Necrosis
- Skin changes

Patient characteristics (gender, mean age): Gender or ages not reported for all studies.
Of studies with these characteristics report: 1,229 female, 142 male, 50 years of age
Number per group: 1,842

Observed adverse effects: Most common reported AEs were persistent swelling or redness, lumpiness at the injection site, and granuloma or enlargement of the implant. Complication rates ranged from 3% to 10% depending on the reviewed study.

Timing of adverse effects: 55% of all reported AEs occurred within the first year of implant. An additional 35% of reported AEs occurred up to 5 years after the injection (10% at year 2, 10% at year 3, 5% at year 4, and 10% at year 5). These data indicate that the chronic inflammatory response to PMMA injection may be active for years after injection. The primary chronic adverse event was formation of granulomas.

Factors that predict response: "Although the exact potential triggers to enhance the high activity inflammatory response and develop a late complication are not fully described, some factors are discussed to be related to chronic inflammation, mainly the product origin, excessive injected volume, features of the vehicle, concentration, size of the microspheres, area and depth of filling, experience of the professional and use of needle instead of cannula."

AEs = adverse events; NR = not reported; PMMA = polymethyl methacrylate; RCT = randomized controlled trial

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

Local Response/Toxicity

Source Citation: Hristov et al. 2020[35]

Study Design: Nonrandomized comparison study
Device or Material: Soft relining material for dentures: PMMA compared with vinyl-polysiloxane
Contract Duration: 3 years
Dose: NR
Frequency/Duration: Single administration
Response:
- Inflammation

Patient characteristics (gender, mean age): 11 male and 12 female; Mean age NR
Number per group: 23 patients and 27 dentures. 16 PMMA, 11 vinyl-polysiloxane
Observed adverse effects: "All patients included in this study stated that the retention and the stability of their dentures improved and no signs of soreness or redness were noticed."
Timing of adverse effects: No adverse events after 3 years
Factors that predict response: NR

Source Citation: Syed et al. [34]

Study Design: Systematic review
Device or Material: Dental resins and dentures
Contract Duration: NR
Dose: 0.4 mg/m^3
Frequency/Duration: Single administration
Response: Delayed allergic hypersensitivity
Patient characteristics (gender, mean age): NR
Number per group: NR
Observed adverse effects: Monomer leeching cause allergic dermatitis in dentists and dental laboratory technicians. Prevalence of contact allergy to methyl methacrylate is 1%.
Timing of adverse effects: NR, postulate that allergic reaction associated with repeated exposure
Factors that predict response: NR

NR = not reported

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

Local Response/Toxicity

Source Citation: Las et al. 2021[12]

Study Design: Systematic review
Device or Material: PMMA
Contract Duration: During surgery to 45 years
Dose: NR
Frequency/Duration: Single administration
Response:
- Hypersensitivity and allergic reactions
- Chronic aseptic inflammation
- Neurotoxicity

Patient characteristics (gender, mean age): Age range: 16 to 68 years, some studies did not report age. 6 male and 7 female, some studies did not report gender.
Number per group: 18 patients from 10 studies had reports of PMMA-related toxicity; 11% of patients included in the 10 studies.
Observed adverse effects: Hypersensitivity and allergic reactions in 4 patients (1 death). Chronic aseptic inflammation in 8 patients. Neurotoxicity in 6 patients
Timing of adverse effects: Range: during surgery to 45 years.
Factors that predict response: "For acrylic-based materials (polymer or PMMA), residual monomer generates toxicity. In vitro studies have demonstrated the cytotoxic effects of the PMMA monomer. The number of residual monomers formed, and the subsequent level of cytotoxicity, relate to the method of polymerization." See references in publication.

Source Citation: Hohne et al. 2018 [37]

Study Design: Retrospective nonrandomized comparison study
Device or Material: Cranioplasty reshapes: PMMA compared to titanium
Contract Duration: Mean of 198 days, longest follow up was 5.5 years
Dose: NR
Frequency/Duration: Single administration
Response:
- Infection
- Epidural hematoma
- CSF fistula
- Tissue necrosis

Patient characteristics (gender, mean age): Preformed titanium group: 33 men, 27 women, 54 years
Freehand molded PMMA group: 38 men, 22 women, 46 years
Number per group: 60
Observed adverse effects: PMMA group: infection in 6 patients, hemorrhage in 6 patients, CSF fistula in 3 patients, tissue necrosis in 1 patient, neuropathy in 1 patient
Titanium group: infection in 5 patients, hemorrhage in 4 patients, CSF fistula in 2 patients
Timing of adverse effects: Range: during surgery to 5.5 years
Factors that predict response: NR

Source Citation: Leao et al. [8]

Study Design: Systematic review
Device or Material: PMMA compared to autologous bone and titanium mesh
Contract Duration: Range from 63 days to 54.3 months
Dose: NR
Frequency/Duration: Single administration

Response:
- Infection
- Epidural hematoma
- Dehiscence
- Seroma
- Material displacement
- Thermal sensitivity

Patient characteristics (gender, mean age): NR
Number per group: PMMA (n = 379), autologous bone (n = 408), titanium (n = 151)
Observed adverse effects: "Of the analyzed materials, autologous bone presented a complication rate of 17.44% (108), PMMA of 14.1% (61), titanium of 8.6% (13), ceramic of 5.88% (1), hydroxyapatite of 32.5% (13), and PMMA + titanium of 0% (0). Among all complications (n = 205), infection was the most prevalent (113, 55.1%), followed by hematoma (36, 17.5%), dehiscence (17, 8.2%), seroma (9, 4.4%), material displacement (7, 3.4%), thermal sensitivity (2, 1%), bone resorption (2, 1%), and edema (1, 0.5%). There was no significant difference in complication rates between PMMA and autologous bone or PMMA and titanium mesh."
Timing of adverse effects: NR
Factors that predict response: "Infection was the most prevalent complication. In several studies, infection may have occurred as a result of technical errors during surgery. This result may be related not only to the type of material but also to different risk factors in patients, such as hypertension and diabetes, systemic infection, lower hemoglobin levels, motor deficits, and the interval between craniotomy and cranioplasty.
"Although PMMA is considered a good choice for cranioplasty, it features some disadvantages, such as lack of adhesion to organic tissues, which increase the risk of infection and exposure to the material.
"Another disadvantage is the release of residual monomers by chemical activation of PMMA, which creates a possibility of tissue damage."

Source Citation: Oliver et al. 2019[38]
Study Design: Systematic Review
Device or Material: Cranial implants: PMMA, titanium, PEEK, Norian
Contract Duration: Range of 26.8 to 41.0 months, mean of 40.2 months
Dose: N/A
Frequency/Duration: Single administration
Response:
- Infection
- Local complication
- Graft failure

Patient characteristics (gender, mean age): 1,123 male, 440 female (some included studies did not specify gender), mean age, 40.1 years
Number per group: 1,429 titanium, 1,459 PMMA, 221 PEEK, 483 Norian
Observed adverse effects: PMMA implants were associated with a significantly higher infection rate. (7.95%, p = 0.0266) compared with all other implant types (6.05%). Although statistically significant, the difference is small.
Timing of adverse effects: NR, however, studies with follow-ups <12 months were excluded from review.
Factors that predict response: "All studies included in the analysis retrospectively review outcomes, increasing the likelihood for selection and reporting bias. Follow-up also varied significantly across studies, which may lead to an underestimation in the incidence of outcomes. We were unable to stratify calculations by age, sex, severity of injury, comorbidities, and other variables, which may have influenced our results."

Source Citation: Zaed et al. 2019[36]
Study Design: Systematic Review
Device or Material: 3D printed custom-made cranial implants: PMMA, titanium, PEEK, hydroxyapatite (HA)
Contract Duration: Mean follow-up: 27 months
Dose: N/A

Frequency/Duration: Single administration
Response:

- Infection
- Fractures
- Prosthesis displacement
- Epidural hematoma
- Fluid collection

Patient characteristics (gender, mean age): 787 male, 513 female (not all included studies reported gender), mean age, 40 years
Number per group: 649 titanium, 298 PMMA, 233 PEEK, 508 HA
Observed adverse effects: 348 complications recorded out of 1,688 report patients (20.64%) with 210 surgical revisions.
Sixty-one patients (3.62%) reported postoperative fluid collection and 12 of them required surgical revision (19.67%). 38 (5.86%) fluid collections were recorded in the titanium group and 7 of them (1.08%) required revision surgery. One (0.34%) fluid collection was observed in the PMMA group with 1 (0.34%) surgical revision, 11 (4.72%) fluid collections were recorded in the PEEK group, 4 (1.71%) of them required revision surgery and 11 (2.17%) fluid collections were observed in the HA group, with no revisions performed (0%).
Postoperative infections were recorded in 151 patients (8.96%): 66 (10.17%) infections were recorded in the titanium group, 31 infections (10.47%) in the PMMA group, 17 (7.29%) in the PEEK group and 37 (7.3%) in the HA group. 124 patients (7.35%) required a second surgery for postoperative infections: 50 cases in the titanium group (7.7%), 30 in the PMMA group (10.14%), 14 in the PEEK group (6.01%), and 30 in the HA group (5.9%).
PMMA showed a lower rate of postoperative epidural hematoma compared with other materials and a lower rate of infection compared to titanium.
Timing of adverse effects: NR
Factors that predict response: "Due to the lack of porosity, PMMA implants cannot be infiltrated by new bone tissue; they interfere with osteoconduction and vascularization, and do not interact with the surrounding tissue.
"What we previously said regarding therapeutic cranioplasty needing an ideal material is unfortunately still true but we have to start using the available different heterologous cranioplasty for different patients. The choice of material has to be based on the clinical data of our patients, like decompression size, patient age, presence of seizures, possibility of recovery, good long-term outcome associated with a cost analysis."

Appendix E. References

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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.