

RESPONSIBLE USE OF HIGH-RISK MEDICAL DEVICES: THE EXAMPLE OF 3D PRINTED MEDICAL DEVICES

APPENDIX 1



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APPENDIX 1

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COLOPHON

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- **Subsequently, a (final) version was submitted to the validators. The validation of the report results from a consensus or a voting process between the validators. The validators did not co-author the scientific report and did not necessarily all three agree with its content.**
- **Finally, this report has been approved by the Executive Board.**
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1. SEARCH STRATEGIES MEDICAL LITERATURE

Date	21-03-2017
Database	OVID Medline
Search Strategy	1 Printing, Three-Dimensional/ (1095) 2 ((3D or 3-Dimensional or Three-Dimensional) adj1 print*).mp. (1727) 3 (3D or 3-Dimensional or Three-Dimensional).mp. and Printing/ (193) 4 (3D adj3 implan*).mp. (266) 5 (custom-made adj5 reconstruct*).mp. (85) 6 stereolithography.mp. (433) 7 reverse engineering.mp. (816) 8 patient-specific implant*.mp. (96) 9 rapid prototyp*.mp. (1524) 10 or/1-9 (4545) 11 randomized controlled trial.pt. (456559) 12 controlled clinical trial.pt. (93330) 13 randomized.ab. (348329) 14 placebo.ab. (171210) 15 clinical trials as topic.sh. (184480) 16 randomly.ab. (239541) 17 trial.ti. (155443) 18 or/11-17 (1025268) 19 exp animals/ not humans.sh. (4363013) 20 18 not 19 (939063) 21 meta-analysis.mp,pt. or review.pt. or search:.tw. (2364606) 22 20 or 21 (3155380) 23 10 and 22 (553)
Note	



Date	21-03-2017
Database	Embase
Search Strategy	#1. 'three dimensional printing'/exp (1500) #2. 3d:ti,ab OR '3 dimensional':ti,ab OR 'three dimensional':ti,ab AND print*:ti,ab (3219) #3. 'printing'/exp AND (3d:ti,ab OR '3 dimensional':ti,ab OR 'three dimensional':ti,ab) (846) #4. (3d NEAR/3 implan*):ti,ab (463) #5. ('custom made' NEAR/5 reconstruct*):ti,ab (137) #6. stereolithography:ti,ab (571) #7. 'reverse engineering':ti,ab (1023) #8. 'patient specific':ti,ab AND implant*:ti,ab (1281) #9. rapid:ti,ab AND prototyp*:ti,ab (4429) #10. #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 (11246) #11. #10 AND ([cochrane review]/lim OR [systematic review]/lim OR [meta analysis]/lim OR [controlled clinical trial]/lim OR [randomized controlled trial]/lim) AND ([article]/lim OR [article in press]/lim OR [review]/lim) AND ([dutch]/lim OR [english]/lim OR [french]/lim) AND ([embase]/lim OR [medline]/lim) (117)
Note	

Date	21-03-2017			
Database	Cochrane Library			
Search Strategy	#1	MeSH descriptor: [Printing, Three-Dimensional] explode all trees		12
	#2	3D or 3-Dimensional or Three-Dimensional:ti,ab	4191	
	#3	print*:ti,ab	1766	
	#4	MeSH descriptor: [Printing] 1 tree(s) exploded	15	
	#5	#3 or #4	1767	
	#6	#2 and #5	41	
	#7	#1 or #6	45	
Note				



Date	21-03-2017
Database	PubMed
Search Strategy	"Printing, Three-Dimensional"[Mesh] OR ((3D[Text Word] OR 3-Dimensional[Text Word] OR Three-Dimensional[Text Word]) AND ("Printing"[Mesh] OR print*[Text Word])) OR (3D[Text Word] AND implant*[Text Word]) OR (custom-made[Text Word] AND reconstruct*[Text Word]) OR stereolithography[Text Word] OR reverse engineering[Text Word] OR patient-specific implant*[Text Word] OR rapid prototyp*[Text Word]
Note	



2. SELECTION RESULTS

On March 21, 2017 a search was performed to identify publications regarding the use of 3D printing. OVID MEDLINE (including PreMedline), PubMed, Embase and the Cochrane Library were searched.

551, 854, 117 and 45 potentially relevant references were identified, respectively (Figure 1). After de-duplication (N=450) and removing references published in an excluded language (other than English, French and Dutch; N=107) 1010 unique references remained. Based on title and abstract 975 references were excluded. Of the remaining 35 references, 17 references were included based on full-text evaluation and 18 references were excluded with reason (Figure 1 – Study flow of selection).

One systematic review (published after March 2017) was added by experts after the search.

Figure 1 – Study flow of selection

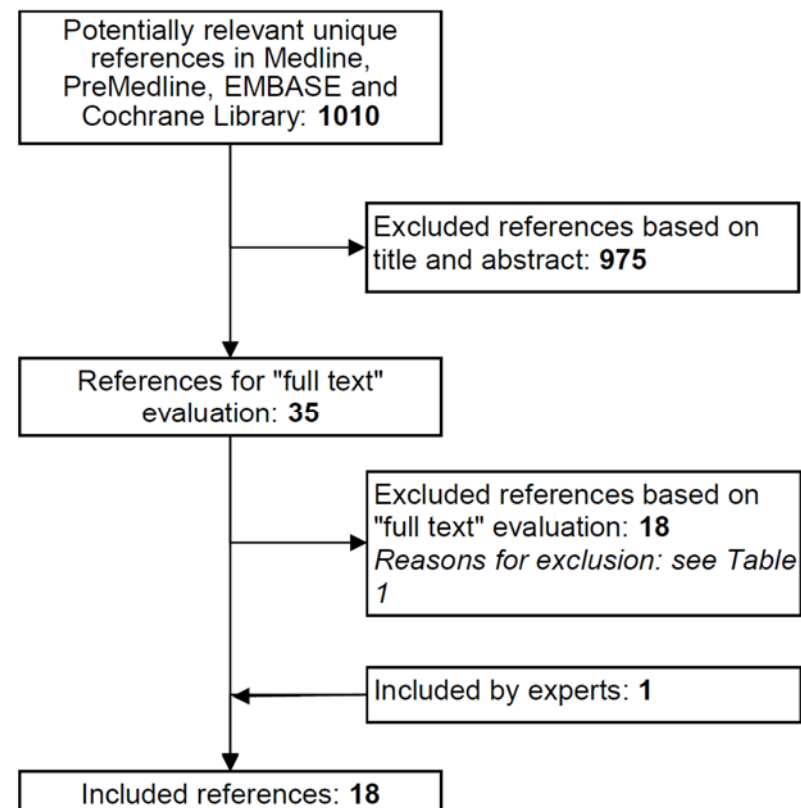


**Table 1 – Excluded references**

Reference	Reason for exclusion
Ayoub N, Ghassemi A, Rana M, Gerressen M, Riediger D, Hölzle F, et al. Evaluation of computer-assisted mandibular reconstruction with vascularized iliac crest bone graft compared to conventional surgery: A randomized prospective clinical trial. <i>Trials</i> . 2014;15(1).	RCT included in SR
Bidra AS, Taylor TD, Agar JR. Computer-aided technology for fabricating complete dentures: systematic review of historical background, current status, and future perspectives. <i>Journal of Prosthetic Dentistry</i> . 2013;109(6):361-6.	Narrative review based on PubMed search
Bizzotto N, Tami I, Santucci A, Adani R, Poggi P, Romani D, et al. 3D printed replica of articular fractures for surgical planning and patient consent: a two years multi-centric experience. <i>3D printing in medicine</i> . 2017;2(1) (no pagination).	No RCT; no 3D implants
Chen X, Xu L, Wang Y, Hao Y, Wang L. Image-guided installation of 3D-printed patient-specific implant and its application in pelvic tumor resection and reconstruction surgery. <i>Computer methods and programs in biomedicine</i> . 2016;125:66-78.	Narrative review
Choi JW, Kim N. Clinical application of three-dimensional printing technology in craniofacial plastic surgery. <i>Arch Plast Surg</i> . 2015;42(3):267-77.	Narrative review based on PubMed search
de Farias TP, Dias FL, Galvao MS, Boasquevisque E, Pastl AC, Albuquerque Sousa B. Use of prototyping in preoperative planning for patients with head and neck tumors. <i>Head & Neck</i> . 2014;36(12):1773-82.	RCT included in SR
Fan H, Fu J, Li X, Pei Y, Li X, Pei G, et al. Implantation of customized 3-D printed titanium prosthesis in limb salvage surgery: a case series and review of the literature. <i>World Journal of Surgical Oncology</i> . 2015;13(308):04.	Narrative review based on PubMed search
Hoang D, Perrault D, Stevanovic M, Ghiassi A. Surgical applications of three-dimensional printing: a review of the current literature & how to get started. <i>Ann Transl Med</i> . 2016;4(23):456.	Narrative review based on PubMed search
Jain MK, Manjunath KS, Bhagwan BK, Shah DK. Comparison of 3-dimensional and standard miniplate fixation in the management of mandibular fractures. <i>J Oral Maxillofac Surg</i> . 2010;68(7):1568-72.	No 3D printing
Kotela A, Kotela I. Patient-specific computed tomography based instrumentation in total knee arthroplasty: a prospective randomized controlled study. <i>Int. Orthop</i> . 2014.	RCT included in SR
Kozakiewicz M, Szymor P. Comparison of pre-bent titanium mesh versus polyethylene implants in patient specific orbital reconstructions. <i>Head & Face Medicine</i> . 2013;9(32):29.	RCT included in SR
Parratte S, Blanc G, Boussemart T, Ollivier M, Le Corroller T, Argenson JN. Rotation in total knee arthroplasty: No difference between patient-specific and conventional instrumentation. <i>Knee Surg. Sports Traumatol. Arthroscopy</i> . 2013;21(10):2213-9.	RCT included in SR
Roh YW, Kim TW, Lee S, Seong SC, Lee MC. Is TKA using patient-specific instruments comparable to conventional TKA? A randomized controlled study of one system knee. <i>Clin. Orthop. Relat. Res</i> . 2013;471(12):3988-95.	RCT included in SR
Sariali E, Mauprivez R, Khiami F, Pascal-Mousselard H, Catonne Y. Accuracy of the preoperative planning for cementless total hip arthroplasty. A randomised comparison between three-dimensional computerised planning and conventional templating. <i>Orthop Traumatol Surg Res</i> . 2012;98(2):151-8.	No 3D printing



Reference	Reason for exclusion
Torabi K, Farjood E, Hamedani S. Rapid Prototyping Technologies and their Applications in Prosthodontics, a Review of Literature. J Dent (Shiraz). 2015;16(1):1-9.	Narrative review based on Medline search
Williams LR, Fan KF, Bentley RP. Custom-made titanium cranioplasty: early and late complications of 151 cranioplasties and review of the literature. International Journal of Oral & Maxillofacial Surgery. 2015;44(5):599-608.	Narrative review based on Medline search
Zhang YZ, Chen B, Lu S, Yang Y, Zhao JM, Liu R, et al. Preliminary application of computer-assisted patient-specific acetabular navigational template for total hip arthroplasty in adult single development dysplasia of the hip. The International Journal Of Medical Robotics + Computer Assisted Surgery: MRCAS. 2011;7(4):469-74.	RCT included in SR
Zheng Y-x, Yu D-f, Zhao J-g, Wu Y-l, Zheng B. 3D Printout Models vs. 3D-Rendered Images: Which Is Better for Preoperative Planning? J Surg Educ. 2016;73(3):518-23.	No clinical study



3. QUALITY APPRAISAL

3.1. Quality appraisal tools

3.1.1. Systematic reviews

AMSTAR criteria were used to assess systematic reviews (Table 2).

Table 2 – AMSTAR checklist

Question	Answer
1. Was an 'a priori' design provided? The research question and inclusion criteria should be established before the conduct of the review.	☐ Yes ☐ No ☐ Can't answer ☐ Not applicable
2. Was there duplicate study selection and data extraction? There should be at least two independent data extractors and a consensus procedure for disagreements should be in place.	☐ Yes ☐ No ☐ Can't answer ☐ Not applicable
3. Was a comprehensive literature search performed? At least two electronic sources should be searched. The report must include years and databases used (e.g. Central, EMBASE, and MEDLINE). Key words and/or MESH terms must be stated and where feasible the search strategy should be provided. All searches should be supplemented by consulting current contents, reviews, textbooks, specialized registers, or experts in the particular field of study, and by reviewing the references in the studies found.	☐ Yes ☐ No ☐ Can't answer ☐ Not applicable
4. Was the status of publication (i.e. grey literature) used as an inclusion criterion? The authors should state that they searched for reports regardless of their publication type. The authors should state whether or not they excluded any reports (from the systematic review), based on their publication status, language etc.	☐ Yes ☐ No ☐ Can't answer ☐ Not applicable
5. Was a list of studies (included and excluded) provided? A list of included and excluded studies should be provided.	☐ Yes ☐ No ☐ Can't answer ☐ Not applicable
6. Were the characteristics of the included studies provided?	☐ Yes



Question	Answer
In an aggregated form such as a table, data from the original studies should be provided on the participants, interventions and outcomes. The ranges of characteristics in all the studies analyzed e.g. age, race, sex, relevant socioeconomic data, disease status, duration, severity, or other diseases should be reported.	☐ No ☐ Can't answer ☐ Not applicable
7. Was the scientific quality of the included studies assessed and documented? 'A priori' methods of assessment should be provided (e.g., for effectiveness studies if the author(s) chose to include only randomized, double-blind, placebo controlled studies, or allocation concealment as inclusion criteria); for other types of studies alternative items will be relevant.	☐ Yes ☐ No ☐ Can't answer ☐ Not applicable
8. Was the scientific quality of the included studies used appropriately in formulating conclusions? The results of the methodological rigor and scientific quality should be considered in the analysis and the conclusions of the review, and explicitly stated in formulating recommendations.	☐ Yes ☐ No ☐ Can't answer ☐ Not applicable
9. Were the methods used to combine the findings of studies appropriate? For the pooled results, a test should be done to ensure the studies were combinable, to assess their homogeneity (i.e. Chi-squared test for homogeneity, I^2). If heterogeneity exists a random effects model should be used and/or the clinical appropriateness of combining should be taken into consideration (i.e. is it sensible to combine?).	☐ Yes ☐ No ☐ Can't answer ☐ Not applicable
10. Was the likelihood of publication bias assessed? An assessment of publication bias should include a combination of graphical aids (e.g., funnel plot, other available tests) and/or statistical tests (e.g., Egger regression test).	☐ Yes ☐ No ☐ Can't answer ☐ Not applicable
11. Was the conflict of interest stated? Potential sources of support should be clearly acknowledged in both the systematic review and the included studies.	☐ Yes ☐ No ☐ Can't answer ☐ Not applicable

3.1.2. Primary studies for therapeutic interventions

To assess risk of bias of randomised controlled trials, we used Cochrane Collaboration's tool (Table 3).

**Table 3 – Cochrane Collaboration's tool for assessing risk of bias**

Domain	Support for judgement	Review authors' judgement
Selection bias		
Random sequence generation	Describe the method used to generate the allocation sequence in sufficient detail to allow an assessment of whether it should produce comparable groups	Selection bias (biased allocation to interventions) due to inadequate generation of a randomised sequence
Allocation concealment	Describe the method used to conceal the allocation sequence in sufficient detail to determine whether intervention allocations could have been foreseen in advance of, or during, enrolment	Selection bias (biased allocation to interventions) due to inadequate concealment of allocations prior to assignment
Performance bias		
Blinding of participants and personnel Assessments should be made for each main outcome (or class of outcomes)	Describe all measures used, if any, to blind study participants and personnel from knowledge of which intervention a participant received. Provide any information relating to whether the intended blinding was effective	Performance bias due to knowledge of the allocated interventions by participants and personnel during the study
Detection bias		
Blinding of outcome assessment Assessments should be made for each main outcome (or class of outcomes)	Describe all measures used, if any, to blind outcome assessors from knowledge of which intervention a participant received. Provide any information relating to whether the intended blinding was effective	Detection bias due to knowledge of the allocated interventions by outcome assessors
Attrition bias		
Incomplete outcome data Assessments should be made for each main outcome (or class of outcomes)	Describe the completeness of outcome data for each main outcome, including attrition and exclusions from the analysis. State whether attrition and exclusions were reported, the numbers in each intervention group (compared with total randomized participants), reasons for attrition/exclusions where reported, and any reinclusions in analyses performed by the review authors	Attrition bias due to amount, nature or handling of incomplete outcome data
Reporting bias		
Selective reporting	State how the possibility of selective outcome reporting was examined by the review authors, and what was found	Reporting bias due to selective outcome reporting
Other bias		
Other sources of bias	State any important concerns about bias not addressed in the other domains in the tool If particular questions/entries were prespecified in the review's protocol, responses should be provided for each question/entry	Bias due to problems not covered elsewhere in the table



3.2. Quality appraisal results

Quality appraisal of selected systematic reviews

Table 4 shows the results of the risk of bias assessment for the 12 included systematic reviews, using AMSTAR criteria.

Table 4 – Methodological quality of the included systematic reviews (AMSTAR)

Systematic review	A priori study design	Duplicate study selection and data extraction	Comprehensive literature search	Publication status not used as inclusion	List of in- and excluded studies	Characteristics of included studies provided	Study quality assessed and documented	Quality assessment used in conclusions	Appropriate methods to combine findings	Likelihood of publication bias assessed	Conflict of interest stated
Bilgin 2016	?	?	Y	N	N	N	N	N	Not applicable	Not applicable	N
Cavaignac 2015	Y	?	Y	?	N	Y	Y	Y	Y	Y	N
Chao 2017	Y	?	Y	N	N	N	N	N	Not applicable	Not applicable	N
Malik 2015	?	?	Y	?	N	N	N	N	Not applicable	Not applicable	N
Mannan 2016, The Knee	?	Y	Y	Y	N	Y	Y	N	Y	Y	N
Mannan 2016, J Knee Surg	Y	Y	Y	Y	N	Y	Y	N	N	Y	N
Martelli 2016	Y	Y	Y	N	N	Y	N	N	Y	Not applicable	N
Popescu 2016	?	?	Y	N	N	Y	N	N	Y	Not applicable	N
Randazzo 2015	?	?	Y	N	N	Y	N	N	Y	Not applicable	N
Soon 2016	Y	?	N	N	N	N	N	N	Y	Not applicable	N
Tack 2016	?	?	Y	N	N	Y	N	N	Y	Not applicable	N
Thienpont 2017	Y	Y	Y	N	N	Y	Y	Y	N	Y	N
Ursan 2013	?	?	Y	?	N	Y	N	N	Y	Not applicable	N



Quality appraisal of selected RCTs for treatment

Table 5 shows the results of the risk of bias assessment for the 5 included studies.

Table 5 – Risk of bias summary of RCTs

	Boudriau 2016		Shuang 2016		Hendel 2012		Qiu 2017		Yang 2016	
Bias	Judgement	Explanation	Judgement	Explanation	Judgement	Explanation	Judgement	Explanation	Judgement	Explanation
Random sequence generation (selection bias)	Low risk		Unclear risk	Randomly divided, but how	Low risk		Unclear risk	Method not discussed	Unclear risk	Method not discussed
Allocation concealment (selection bias)	Unclear risk	Not reported	Unclear risk	Not reported	Low risk		Unclear risk	Not reported	Unclear risk	Not reported
Blinding of participants and personnel (performance bias): OBJECTIVE OUTCOMES	Low risk		Low risk		Low risk		Low risk		Low risk	
Blinding of participants and personnel (performance bias): SUBJECTIVE OUTCOMES	High risk	Unblinded	Unclear risk	Not reported	High risk	Unblinded	Unclear risk	Not reported	Unclear risk	Not reported
Blinding of outcome assessment (detection bias): OBJECTIVE OUTCOMES	Low risk		Low risk		Low risk		Low risk		Low risk	
Blinding of outcome assessment (detection bias): SUBJECTIVE OUTCOMES	High risk	Unblinded	Unclear risk	"Independent observer"	High risk	Unblinded	Unclear risk	Not reported	Unclear risk	Not reported
Incomplete outcome data (attrition bias)	Low risk		Low risk		Low risk		Unclear risk	Unclear from article	Unclear risk	Unclear from article
Selective reporting (reporting bias)	Low risk		Low risk		Low risk		Unclear risk	Unclear from article	Unclear risk	Unclear from article
Other bias	Low risk		Low risk		Low risk		Low risk		Low risk	



4. EVIDENCE TABLES

4.1. Systematic reviews

Table 6 – Evidence table of systematic reviews regarding the effect of 3D printing

Bilgin 2016	
Methods	
• Design	Systematic review
• Source of funding and competing interest	None
• Search date	1987-2014
• Searched databases	PubMed/MEDLINE, ScienceDirect, Google Scholar, and Web of Science databases
• Included study designs	All
• Number of included studies	N=40
• Statistical analysis	Not applicable
Patient characteristics	
• Patient & disease characteristics	Not reported in detail
Interventions: Removable dentures fabricated using computer-aided design/computer-aided manufacture (CAD/CAM) and rapid prototyping (RP)	
Results: narrative presentation	
Limitations and other comments	
• Limitations	• Unclear if duplicate selection and data extraction • English literature only • No quality appraisal of included studies



Cavaignac 2015	
Methods	
• Design	Systematic review and meta-analysis
• Source of funding and competing interest	P. Chiron is a consultant for Zimmer, Smith & Nephew and Sanofi, and has received royalties from Zimmer and Integra. Jean Michel Laffosse is a consultant for Tornier and Stryker. The other authors have no conflict of interest to disclose.
• Search date	May 2014
• Searched databases	Medline, EMBASE, SciSearch, OVID Database and Cochrane Central Register
• Included study designs	RCTs, quasi-RCTs, non-randomized prospective or historical cohorts
• Number of included studies	N=15
• Statistical analysis	• Forest plots as well as Cochran's heterogeneity statistic and Higgins' I^2 coefficients were used to assess heterogeneity across studies. A p value less than 0.1 or I^2 above 50 % was considered suggestive of statistical heterogeneity, prompting random effects modeling • Mean differences between the PSCB and MI groups were estimated using the inverse variance approach with 95% confidence intervals • The risk ratio (RR) for more than 3° misalignment was calculated for PSCB versus MI procedures • Funnel plots were used to assess small-study effects • Review Manager software (version 5.2, The Cochrane Collaboration, Copenhagen, Denmark) was used for all statistical analyses
Patient characteristics	
• Patient & disease characteristics	Patients undergoing total knee arthroplasty
Interventions	
• Intervention group	Patient-specific cutting blocks
• Control group	Standard instrumentation
Results (RCTs only, N=6)	
• Leg axis alignment	MD = -0.02 (95%CI -0.53 to 0.48)
• >3° misalignment in hip-knee-ankle	RR = 1.01 (0.71-1.44)
• >3° misalignment in femoral coronal angle	RR = 0.72 (0.41-1.28)
• >3° misalignment in tibial coronal angle	RR = 1.50 (0.53-4.24)



- **>3° misalignment in femoral sagittal angle** RR = 1.15 (0.85-1.55)
- **>3° misalignment in tibial sagittal angle** RR = 2.21 (0.86-5.63)
- **Femoral component rotation** MD = -0.62 (-1.23 to -0.02)
- **>3° misalignment in femoral rotation angle** RR = 0.91 (0.57-1.46)

Limitations and other comments

- **Limitations**
 - Unclear if duplicate data extraction
 - Unclear if status of publication was used as inclusion criterion

Chao 2017

Methods

- **Design** Systematic review
- **Source of funding and competing interest** None
- **Search date** 1990-2016
- **Searched databases** Medline, Embase
- **Included study designs** All
- **Number of included studies** N=34
- **Statistical analysis** Not applicable

Patient characteristics

- **Patient & disease characteristics** Patients undergoing anaesthesia

Interventions: 3D printing within the field of anaesthesia

Results: narrative presentation

Limitations and other comments

- **Limitations**
 - Unclear if duplicate data extraction
 - English literature only
 - No quality appraisal of included studies



Malik 2015	
Methods	
• Design	Systematic review
• Source of funding and competing interest	None
• Search date	June 2014
• Searched databases	Medline, Embase, PsycInfo, PubMed
• Included study designs	All
• Number of included studies	N=93
• Statistical analysis	Not applicable
Patient characteristics	
• Patient & disease characteristics	Patients undergoing surgery
Interventions: 3D printing in surgery	
Results: narrative presentation	
Limitations and other comments	
• Limitations	• Unclear if duplicate data extraction • Unclear if status of publication was used as inclusion criterion • No quality appraisal of included studies

Mannan 2016, The Knee	
Methods	
• Design	Systematic review and meta-analysis
• Source of funding and competing interest	Not reported
• Search date	2000-2014
• Searched databases	Pubmed, the Cochrane Collaboration Trial Registry and Library, MEDLINE and EMBASE; search for grey literature
• Included study designs	RCTs
• Number of included studies	N=6
• Statistical analysis	• Where appropriate, a random-effects model meta-analysis was performed to evaluate the clinical primary outcomes. Meta-analysis was deemed appropriate in the absence of clinical and statistical heterogeneity. Clinical heterogeneity was assessed



	through observation of data extraction tables while statistical heterogeneity between studies was evaluated with χ^2 with demonstration of values for P and I^2, $P < 0.1$ and $I^2 > 50\%$ indicating heterogeneity • Deviance from a post-operative neutral mechanical axis was measured as the proportion of three degrees outliers • RevMan 5.0 (The Cochrane Collaboration) was used for purposes of statistical analysis • For dichotomous variables, odds ratio (OR) and 95% confidence intervals (CI) were calculated and graphical output was documented by forest plots • A funnel plot was constructed to assess small sample size publication bias for the primary outcome measure • A sensitivity analysis was undertaken of high quality studies (Detsky score ≥ 16) on meta-analysis.
Patient characteristics	
• Patient & disease characteristics	Patients undergoing total knee arthroplasty
Interventions	
• Intervention group	Patient-specific instrumentation
• Control group	Standard instrumentation
Results	
• >3° misalignment in femoral rotation angle	OR = 0.40 (95%CI 0.16-0.95)
Limitations and other comments	
• Limitations	-

Mannan 2016, J Knee Surg

Methods	
• Design	Systematic review and meta-analysis
• Source of funding and competing interest	Not reported
• Search date	2000-2015
• Searched databases	PubMed/Medline, Embase, CENTRAL, Cochrane Library; trial registers, ISI Web of Knowledge; gray literature
• Included study designs	RCTs, prospective comparative studies
• Number of included studies	N=8
• Statistical analysis	• Clinical heterogeneity was assessed through observation of data extraction tables while statistical heterogeneity between studies was evaluated with χ^2 with demonstration of values for P and I^2, $P < 0.1$ and $I^2 > 50\%$ indicating heterogeneity. In the absence of statistical heterogeneity, fixed effects model was used



- RevMan 5.0 (The Cochrane Collaboration) was used for purposes of statistical analysis
- For continuous variables, odds ratio (OR) and 95% confidence intervals (CI) were calculated and graphical output was documented by forest plots
- A funnel plot was constructed to assess small sample size publication bias for the primary outcome measure

Patient characteristics

- **Patient & disease characteristics** Patients undergoing total knee arthroplasty

Interventions

- **Intervention group** Patient-specific instrumentation
- **Control group** Standard instrumentation

Results

- **Knee Society Score (Function)**
 - At 3 months: MD = 2.11 (95%CI -0.31 to 4.54)
 - At 6 months: MD = 6.12 (-17.43 to 29.68)
 - At 12-24 months: MD = -0.21 (-9.31 to 8.88)
- **Knee Society Score (Knee)**
 - At 3 months: MD = 0.32 (-2.21 to 2.84)
 - At 6 months: MD = 5.04 (-6.37 to 16.45)
 - At 12-24 months: MD = 0.90 (-6.15 to 7.95)
- **Postoperative range of movement** MD = 3.72 (-0.46 to 7.91)

Limitations and other comments

- **Limitations**
 - Inappropriate meta-analysis: mixing of study designs

Martelli 2016**Methods**

- **Design** Systematic review
- **Source of funding and competing interest** No funding, conflicts of interest not reported
- **Search date** 2005-2015
- **Searched databases** PubMed, Embase
- **Included study designs** All
- **Number of included studies** N=158
- **Statistical analysis** Not applicable



Patient characteristics

- **Patient & disease characteristics** Patients undergoing surgery

Interventions: 3D printing in surgery

Results: narrative presentation

Limitations and other comments

- **Limitations**
 - French and English literature only
 - No quality appraisal of included studies

Popescu 2016

Methods

- **Design** Systematic review
- **Source of funding and competing interest** No competing interests; funded by the Partnerships in Priority Areas Programme – PN II of MEN – UEFISCDI, through Agreement 5/2014
- **Search date** Dec 2014
- **Searched databases** PubMed, Springer, Elsevier, SearchMedica
- **Included study designs** All
- **Number of included studies** N=61
- **Statistical analysis** Not applicable

Patient characteristics

- **Patient & disease characteristics** Patients undergoing orthopaedic surgery

Interventions: patient-specific surgical orthopaedics guides

Results: narrative presentation

Limitations and other comments

- **Limitations**
 - Unclear if duplicate data extraction
 - English literature only
 - No quality appraisal of included studies

**Randazzo 2015****Methods**

- **Design** Systematic review
- **Source of funding and competing interest** None
- **Search date** Dec 2015
- **Searched databases** Compendex, Scopus, PubMed
- **Included study designs** All
- **Number of included studies** N=36
- **Statistical analysis** Not applicable

Patient characteristics

- **Patient & disease characteristics** Patients undergoing neurosurgery

Interventions: 3D printing**Results:** narrative presentation**Limitations and other comments**

- **Limitations**
 - Unclear if duplicate data extraction and selection
 - English literature only
 - No quality appraisal of included studies

Soon 2016**Methods**

- **Design** Systematic review
- **Source of funding and competing interest** None
- **Search date** 2006-2016
- **Searched databases** Medline/PubMed
- **Included study designs** All
- **Number of included studies** N=6
- **Statistical analysis** Not applicable

**Patient characteristics**

- **Patient & disease characteristics** Patients undergoing hepatic resection

Interventions: 3D haptic modelling for preoperative planning

Results: narrative presentation

Limitations and other comments

- **Limitations**
 - Unclear if duplicate data extraction
 - English literature only
 - No quality appraisal of included studies

Tack 2016**Methods**

- **Design** Systematic review
- **Source of funding and competing interest** Supported by a research grant from the 'Vlaams Agentschap Ondernemerschap' and other partners in the consortium, Materialise N.V., Mobelife N.V., Melotte N.V. and Layerwise N.V.; no financial competing interests
- **Search date** Dec 2015
- **Searched databases** Web of Science, PubMed, Embase
- **Included study designs** Controlled trials and case series of minimum four cases
- **Number of included studies** N=227
- **Statistical analysis** Not applicable

Patient characteristics

- **Patient & disease characteristics** Medical setting in general

Interventions: 3D printing in general

Results: narrative presentation

Limitations and other comments

- **Limitations**
 - Unclear if duplicate data extraction
 - English literature only
 - No quality appraisal of included studies

**Thienpont 2017****Methods**

- **Design** Systematic review and meta-analysis
- **Source of funding and competing interest** Funded by Zimmer Biomet (Winterthur, Switzerland); competing interests reported in online version
- **Search date** 2011-2015
- **Searched databases** PubMed, Embase
- **Included study designs** RCTs and cohort studies
- **Number of included studies** N=44
- **Statistical analysis**
 - Data were summarized as the ratio of relative risk or the difference between means
 - For studies that did not report standard deviations, it was calculated from p values, confidence intervals, or standard errors. If such information was not available, the reviewers contacted the corresponding authors for additional information
 - Random-effect models were used throughout because of the anticipated heterogeneity. However, analyses that included <10 studies were performed with use of fixed-effect models according to Mantel and Haenszel.
 - Meta-analysis of proportions was performed after a Freeman-Tukey (double arcsine) transformation of the data. The Miller equation was used for the corresponding back-transformation.
 - Study heterogeneity was quantified using the I² statistic. To explore the source of heterogeneity, meta-regression analysis was performed, using the log-transformed odds ratio for binary variables or the difference in means for continuous outcome data as dependent variables. For this analysis, the manufacturer, baseline risk of malalignment, study design (randomized versus nonrandomized), region where the study was conducted (Europe versus other), and Detsky Quality Assessment Scale were selected as covariates in the regression model. The primary assessment used the restricted maximum likelihood with random-effect weighting and the Hartung-Knapp modification. Meta-regression analysis was only considered when at least 20 studies were available for analysis. Methods of analysis and covariates in the meta-regression were specified before study commencement.
 - Publication bias was investigated for outcomes with at least 10 included studies. Graphically assessed funnel plots were evaluated for the presence of data and the Harbord modified test for binary outcome variables to test for small-study effects. If publication bias was thought to be present, a trim-and-fill method was used to adjust for publication bias.
 - Sensitivity analyses were conducted to assess the potential impact of modeling assumptions (fixed versus random effect) and the impact of imputation of missing data on the study findings.
 - The level of significance was set at $p < 0.05$. All statistical analyses were carried out using R software (version 3.2.3; R Foundation for Statistical Computing) with use of the Metafor package.

Patient characteristics

- **Patient & disease characteristics** Patients undergoing total knee arthroplasty

Interventions



• Intervention group	Patient-specific instrumentation
• Control group	Standard instrumentation
Results: invalid	
Limitations and other comments	
• Limitations	- English, French, German, or Dutch literature only - Mix of RCTs and non-RCTs in meta-analysis

Ursan 2013

Methods

- | | |
|---|-------------------|
| • Design | Systematic review |
| • Source of funding and competing interest | None |
| • Search date | 1990-2012 |
| • Searched databases | PubMed, Embase |
| • Included study designs | All |
| • Number of included studies | N=21 |
| • Statistical analysis | Not applicable |

Patient characteristics

- | | |
|--|----------------------------|
| • Patient & disease characteristics | Medical setting in general |
|--|----------------------------|

Interventions: 3D printing in general

Results: narrative presentation

Limitations and other comments

- | | |
|----------------------|--|
| • Limitations | <ul style="list-style-type: none"> Unclear if duplicate data extraction Unclear if status of publication was used as inclusion criterion No quality appraisal of included studies |
|----------------------|--|



4.2. RCTs

Table 7 – Evidence table of intervention studies regarding the effect of 3D printing

Boudriau 2016	
Methods	
• Design	RCT, open-label, cross-over
• Source of funding and competing interest	Funded by Aprelia Pharmaceuticals Company; authors are full-time employees and/or stockholders of Algorithme Pharma Inc.
• Setting	Healthy subjects; Industry setting, Canada
• Sample size	N=33
• Duration and follow-up	• Inclusion: October 2013 • Median follow-up:
• Statistical analysis	• The natural logarithm(ln) of C_{max}, AUC_{0-T}, and $AUC_{0-\infty}$, and the rank transformation of T_{max} were used for statistical inference • Statistical analyses were performed with an analysis of variance (ANOVA) model and the two-sided 90 %CI of ratio of geometric LSmeans was obtained between both products under fasting conditions (Treatment-1 vs. Treatment-2). Food effect of levetiracetam 3DP fast melt was assessed using the ratio of geometric LSmeans with corresponding 90 % CI calculated from the exponential of the difference between fed and fasting conditions (Treatment-3 vs. Treatment-1) • Statistical analyses were performed using SAS version 9 (SAS Institute, USA). SAS PROC MIXED was used for the ANOVA model. The fixed factors included in the model were the treatment received, the period at which it was given, as well as the sequence in which each treatment was received. A random factor was added for the subject effect (nested within sequence) • Statistical significance was assessed at the two-sided 5 % level
Patient characteristics	
• Eligibility criteria	• Healthy men or non-pregnant women, aged between 18 and 50 years, with a body mass index >18.50 and <30.00 kg/m²
Interventions	
• Control group	Immediate-release, film-coated levetiracetam tablet (B)
• Intervention group	Single 1000-mg administration of the levetiracetam 3DP fast-melt formulation: - In fasting conditions (A) - 30 min after an FDA-compliant, high-fat, high-calorie breakfast (C)
Results	
A vs. B vs. C	
• T max (h)	0.58 vs. 0.58 vs. 4.00
• C max (µg/ml)	33.273 vs. 30.480 vs. 20.481



• AUC_{0-T} (µg/h/ml)	283.689 vs. 274.934 vs. 262.550
• AUC_{0-∞} (µg/h/ml)	292.927 vs. 284.300 vs. 272.565
• T half (h)	7.13 vs. 7.14 vs. 7.19
• Safety	No deaths or serious adverse events; no withdrawals for safety reasons
Limitations and other comments	
• Limitations	- Unclear allocation concealment - Open-label study

Shuang 2016

Methods

• Design	RCT
• Source of funding and competing interest	No competing interests; funding not reported
• Setting	Single university centre, China
• Sample size	N=13
• Duration and follow-up	- Inclusion: Mar – Oct 2014 - Mean follow-up: 10.6m
• Statistical analysis	- Continuous data are presented as mean +/- standard deviation. Categorical data are presented as frequencies. Comparisons were made using Student's t test or a chi-square test - All statistical analyses were performed using SPSS v17.0 software (SPSS, Chicago, IL) - P<0.05 was considered statistically significant

Patient characteristics

• Eligibility criteria	Patients with distal intercondylar humeral fractures (AO type C3)
• Patient & disease characteristics	The mechanisms of injury were falls from height in 5 patients and traffic accidents in 8 patients

Interventions

• Control group	Surgery using conventional plates
• Intervention group	Surgery using 3D-printed plates

Results 3D vs. conventional

• Operative time	70.6 vs. 92.3 min, p=0.026
-------------------------	----------------------------



• Rate of patients with excellent or good elbow function	83.1% vs. 71.4%, NS
• ROM flexion/extension	98 vs. 93, p=0.73
• ROM pronation/supination	160 vs. 167, p=0.528
• Mayo elbow performance score	85 vs. 79, p=0.394
• Safety	- One patient in the conventional group experienced intraoperative traction injury of the ulnar nerve. The injury resolved after 3 months of rehabilitation - No wound infections or other complications were observed
Limitations and other comments	
• Limitations	- Unclear randomization procedure and allocation concealment - Blinding not clearly reported

Hendel 2012**Methods**

• Design	RCT, non-blinded
• Source of funding and competing interest	Competing interests reported in online version; funding not reported
• Setting	Single centre, US
• Sample size	N=31
• Duration and follow-up	Unclear
• Statistical analysis	- Data were statistically analyzed with use of JMP version 9.0.0 software (SAS Institute, Cary, North Carolina) - The absolute difference between the actual outcome and the planned outcome was compared between the standard surgical group and the glenoid positioning system group with use of a Student t test for continuous data and a Fisher exact test for categorical data - Results were considered to be significant at $p < 0.05$

Patient characteristics

• Eligibility criteria	Patients who underwent primary anatomic total shoulder arthroplasty
Interventions	
• Control group	Glenoid component placement with use of conventional computed tomographic scan, preoperative planning, and surgical technique, utilizing instruments provided by the implant manufacturer



• Intervention group	Glenoid component placement with use of novel 3D computed tomographic scan planning software combined with patient-specific instrumentation
Results	Standard vs. PSI
• Average deviation in component placement	• Total offset (mm): 3.4 vs. 2.4 (p=0.11) • Version: 6.9 vs. 4.3° (p=0.11) • Inclination: 11.6 vs. 2.9° (p<0.0001) • Anteroposterior offset (mm): 1.9 vs. 1.0 (p=0.06) • Medial-lateral offset (mm): 1.9 vs. 1.0 (p=0.012) • Superoinferior offset (mm): 2.3 vs. 2.0 (p=0.64) • Roll (mm): 10.2 vs. 6.5 (p=0.13)
• Malpositioned implants	• 75% vs. 27%, p<0.01
• Adverse events	One patient (5.9%) in the standard surgical group experienced a transient partial axillary nerve injury. No patient in the glenoid positioning system group had an adverse event
Limitations and other comments	
• Limitations	• Unblinded

Qiu 2017

Methods	
• Design	RCT
• Source of funding and competing interest	Supported by Shanghai Science and Technology Committee research project 15441900200; competing interests not reported
• Setting	Single centre, China
• Sample size	N=26
• Duration and follow-up	Not reported
• Statistical analysis	• SPSS software was used • Significant difference was defined as p<0.05 • Values were compared with t-test
Patient characteristics	
• Eligibility criteria	• Patients undergoing total knee arthroplasty
Interventions	
• Control group	Conventional instrumentation



• Intervention group	3D printed cutting guides
Results	PSI vs. conventional instrumentation
• Hip-knee-ankle	0.77 vs. 3.13° (p<0.05)
• Frontal femoral component	0.37 vs. 2.35° (p<0.05)
• Frontal tibial component	0.11 vs. 1.09 (p<0.05)
• Lateral tibial component	0.71 vs. 0.66° (p<0.05)
Limitations and other comments	
• Limitations	• Randomization method and allocation concealment not reported • Unclear blinding • Unclear if incomplete outcome data or selective reporting

Yang 2016	
Methods	
• Design	RCT
• Source of funding and competing interest	Funded by the Department of Science and Technology of Guiyang City (20151001) and National Natural Science Foundation (81360232) China; no competing interests
• Setting	Single university centre, China
• Sample size	N=30
• Duration and follow-up	Not reported
• Statistical analysis	• SPSS 17.0 was used for statistical analysis • Data were expressed as mean ± standard deviation • Data comparison between groups was conducted using Student's <i>t</i>-test • Pearson correlation test was used to assess the correlations between the operation time and intraoperative blood loss • P<0.05 was considered as significant
Patient characteristics	
• Eligibility criteria	• Patients with trimalleolar fractures
Interventions	
• Control group	Standard operation
• Intervention group	3D printing assisted-design operation (open reduction and internal fixation)
Results	3D printing vs. no 3D printing



-
- **Operation time** 71 vs. 98 minutes, $p < 0.05$
 - **Intraoperative blood loss** 65 vs. 90 ml, $p < 0.05$
-

Limitations and other comments

- **Limitations**
 - Randomization method and allocation concealment not reported
 - Unclear blinding
 - Unclear if incomplete outcome data or selective reporting
-



5. SEARCH ORIGINALLY FOCUSED ON CUSTOM IMPLANTS

5.1. Search strategies

Date	14-10-2016
Database	OVID Medline
Search Strategy	1 Printing, Three-Dimensional/ (816) 2 ((3D or 3-Dimensional or Three-Dimensional) adj1 print*).mp. (1369) 3 (3D or 3-Dimensional or Three-Dimensional).mp. and Printing/ (181) 4 1 or 2 or 3 (1456)
Note	

Date	12-12-2016
Database	PubMed
Search Strategy	((((3D or 3-Dimensional or Three-Dimensional) AND print*) AND ("2016/01/01"[PDat] : "2016/12/31"[PDat])) OR selective laser sintering OR additive manufacturing OR electron beam melting
Note	

Date	16-12-2016
Database	OVID Medline
Search Strategy	18 (3D adj3 implan*).mp. (259) 19 (custom-made adj5 reconstruct*).mp. (80) 20 stereolithography.mp. (438) 21 reverse engineering.mp. (933) 22 patient-specific implant*.mp. (85) 23 rapid prototyp*.mp. (1562) 24 18 or 19 or 20 or 21 or 22 or 23 (3178)
Note	



Date	14-10-2015
Database	EMBASE
Search Strategy	#1 'three dimensional printing'/exp (1500) #2 3d:ti,ab OR '3 dimensional':ti,ab OR 'three dimensional':ti,ab AND print*:ti,ab (3219) #3 'printing'/exp AND (3d:ti,ab OR '3 dimensional':ti,ab OR 'three dimensional':ti,ab) (814) #4 #1 OR #2 OR #3 (3627) #5 #1 OR #2 OR #3 AND ([article]/lim OR [article in press]/lim OR [review]/lim) AND ([dutch]/lim OR [english]/lim OR [french]/lim) (2427)
Note	

Date	14-10-2015
Database	Cochrane Library
Search Strategy	#1 MeSH descriptor: [Printing, Three-Dimensional] explode all trees (6) #2 3D or 3-Dimensional or Three-Dimensional:ti,ab (3908) #3 print*:ti,ab (1559) #4 MeSH descriptor: [Printing] 1 tree(s) exploded (15) #5 #3 or #4 (1560) #6 #2 and #5 (22) #7 #1 or #6 (24)
Note	



5.2. Selection results

On October 14, December 12 and December 16, 2016 a search was performed to identify publications regarding the use of 3D printing. OVID MEDLINE (including PreMedline), PubMed, Embase and the Cochrane Library were searched.

3907, 1722 and 3178 potentially relevant references were identified, respectively (Figure 1). After de-duplication and removing references published in an excluded language (other than English, French and Dutch) 6978 references remained. Based on title and abstract 6911 references were excluded. Of the remaining 67 references, 24 references were included based on full-text evaluation and 43 references were excluded.

5.3. Results

5.3.1. Overall yield of the search

The search identified one systematic review,¹ one RCT,² one non-randomized comparative study,³ eight case series,⁴⁻¹¹ and thirteen single case reports.¹²⁻¹⁸, Delpont 2012,¹⁹⁻²³.

5.3.2. Evidence by anatomic location

5.3.2.1. Airway

Zopf et al. published a **case report** of an infant with tracheobronchomalacia and severe respiratory distress requiring endotracheal intubation.¹² Despite placement of a tracheostomy tube, mechanical ventilation, and sedation, ventilation that was sufficient to prevent recurring cardiopulmonary arrests could not be maintained. The authors developed a custom-designed and custom-fabricated resorbable airway splint, manufactured from polycaprolactone with the use of a 3D printer. Seven days after placement of the airway splint, weaning from mechanical ventilation was initiated, and 21 days after the procedure, ventilator support was discontinued entirely and the child was discharged home with the tracheostomy in place. One year after surgery, imaging and endoscopy showed a patent left mainstem bronchus. No unforeseen problems related to the splint arised.

5.3.2.2. Chest wall

Two **case reports** described the use of a 3D printed custom-made prosthesis after extensive chest wall resection for a tumour originating from¹³ or invading the chest wall.¹⁴ the first case, titanium powder was melted layer by layer by electron beam melting (EBM) following a digital 3D model.¹³ The postoperative course was uneventful, no major or minor complications occurred after three months of follow-up. In the second case, surgical-grade titanium alloy was used to print the 3D implant.¹⁴ The patient was discharged home 15 days after surgery and the chest CT scan showed a stable reconstruction, with preservation of thoracic morphology and excellent cosmetic results according to the authors.

5.3.2.3. Skull

In one **non-randomized comparative study**, 17 patients who were treated with patient-specific implants (PSI) for cranioplasty of large skull bone defects were compared retrospectively with 16 patients who had their stored bone grafts reimplanted.³ Nine patients received milled titanium implants, and one patient received an electron laser beam-melted titanium implant. The seven most recently operated-on patients received computerized numerical control-milled PEEK (polyether ether ketone) implants. Complication rate (5.9% vs. 43.8%, $p=0.017$) and the rate of necessary reoperations (0% vs. 25%, $p=0.039$) were significantly lower, and the hospital stay was shorter in the PSI group (mean: 6.4 vs. 13.6, $p=0.004$). No significant differences concerning operative time were found (mean total time of surgery: 175 vs. 198 minutes, $p=0.599$).



Brie et al. reported on a **case series** of eight patients who were treated with a custom-made implant for the repair of large and complex craniofacial bone defects (more than 25 cm²).¹¹ The manufacturing process of the implants used a stereolithography technique that produces ceramic implants in hydroxyapatite with 3D shapes derived directly from the scan file of the patient's skull without moulding or machining. The mean operative time was 116.25 minutes. No major complications (infection or fracture of the implant) were observed.

5.3.2.4. Orbita

Two **case series** both included twelve patients with orbital wall and/or floor defects. Stoor et al. included nine patients with an orbital wall fracture and three patients with an orbital wall defect due to a malignant tumour.⁸ EBM of titanium powder was used to produce the final implant. One implant (8%) was rejected due to chemical impurities, two (16%) had a false shape due to incorrect computer-aided design. One implant (8%) was placed incorrectly, two implants (16%) were placed moderately incorrectly. The duration of the pure orbital wall reconstruction (N=10) was on average 77 minutes. Gander et al. included twelve patients with orbital floor and wall fractures.⁹ Individually manufactured titanium implants were used. No visual impairments were reported aside from double vision in terminal positions, which resolved during postoperative care. Reoperation was not required to reposition implants, or to correct displacement of the ocular bulb. In two cases intraoperative reduction of the implant was necessary due to overextension during computer-aided treatment planning.

5.3.2.5. Mandibulla / maxilla

Two **case series** and two **case reports** described the use of 3D printed implants for mandibular and/or maxillary defects. Suojanen et al. included 32 patients needing maxillary correction.⁷ Patient-specific implants were manufactured using titanium alloy. In all cases except one, the surgery was performed as planned. In one patient, the fitting of the designed plates was not acceptable, which probably resulted from error in the osteotomy design generated by the mandible position during CT. Shan et al. included 2 patients with maxillary defects and 2 with mandibular defects.⁶ All patients

underwent reconstruction with 3D printed titanium mesh. A satisfactory contour was achieved in all patients. The rate of concordance between the preoperative design and the postoperative outcome was higher than 81 and 94% within 3 mm for the mandibular and maxillary reconstructions, respectively. There was no evidence of complications. Hatamleh et al. described a 26-year-old male who presented with a left mandibular defect secondary to trauma.¹⁷ A reconstruction plate that connected the condylar head and the mandible was printed in titanium using selective laser sintering technology. The patient recovered uneventfully. Finally, Lee et al. described a 25-year-old woman who presented with a left lateral mandibular defect from the mental foramen to the condyle and a severe maxillary occlusal cant.¹⁶ The left mandibular body had been removed because of a benign tumour during childhood. An artificial mandible was 3D printed with titanium powder using electron beam melting. Postoperative recovery was uneventful with no complications.

5.3.2.6. Nose

Two **case reports** described a patient requiring reconstruction for a nasal defect. Horn et al. described a 36-year-old woman after near-total nasal resection due to a malignant peripheral nerve sheath tumour in the glabellar and nasal regions.¹⁸ After tumour resection, the cartilaginous and bone structures were reconstructed using a dynamic titanium mesh, which was precontoured on a 3D print model of the preoperative situation. No exposure or local infection of the titanium mesh was observed in the follow-up. Routine magnetic resonance tomographic and computed tomographic scans showed no signs of tumor recurrence. Toso et al. described a 64-year-old man with Osler disease who had undergone life-saving embolization of acute bleedings resulting in necrosis with loss of partial nasal soft tissue and nasal septum.²² A patient-specific implant was fabricated with titanium alloy using additive manufacturing and laser melting. No peri-implant soft tissue complications were observed in a follow-up time of 6 months.



5.3.2.7. Teeth

Tunchel et al. **prospectively** included 82 patients who were treated with 110 3D printed titanium dental implants that were fabricated using additive manufacturing.⁴ After 3 years of loading, six implants failed, for an overall implant survival rate of 94.5%. Among the 104 surviving implant-supported restorations, 6 showed complications and were therefore considered unsuccessful, for an implant-crown success of 94.3%.

5.3.2.8. Extremities

Shuang et al. **randomized** 13 patients with distal intercondylar humeral fractures to undergo surgery using either conventional plates (N=7) or 3D-printed plates (N=6).² The 3D-printing group had a significantly shorter mean operative time (70.6 +/- 12.1 min) than the conventional plates group (92.3 +/- 17.4 min; p=0.026)). After a mean follow-up of 10.6 months, there was no significant difference between groups in the rate of patients with good or excellent elbow function, although the 3D-printing group saw a slightly higher rate of good or excellent evaluations (83.1%) compared to the conventional group (71.4%). One patient in the conventional group experienced intraoperative traction injury of the ulnar nerve. The injury resolved after 3 months of rehabilitation. No wound infections or other complications were observed.

Fan et al. reported **three cases** of patients with clavicle Ewing's sarcoma, scapular Ewing's sarcoma, and pelvic chondrosarcoma, respectively.⁵ All three patients received patient-specific prosthesis implantation after tumour resection. Prostheses were manufactured with titanium alloy using EBM. No surgical complications including limb length discrepancy, screw loosening, and implant breakage were observed.

Hamid et al. described a **case** of a 46-year-old woman with a traumatic left open distal intra-articular tibia fracture with substantial distal tibia bone loss at the scene of the injury.¹⁵ Limb salvage was chosen as treatment option, and a custom 3D printed titanium scaffold was implanted. At 13 months after surgery, she complained of only heel pain at the nail insertion site and by 15 months this pain had resolved in its entirety, leaving her pain-free with a visual analogue score of 0 of 10 for pain.

5.3.2.9. Shoulder

Stoffelen et al. reported on a **case** of a 44-year-old woman who presented with a severe glenoid defect 12 years after total shoulder replacement for a septic arthritis.²¹ 3D printing technology was used to create a custom-made titanium glenoid implant. The postoperative course was uneventful at 2.5 years of follow-up.

5.3.2.10. Pelvis

One **case series** and three **case reports** described the use of 3D printed implants for pelvic defects. Colen et al. included six patients with severe acetabular bone defects in combination with failure of a total hip arthroplasty.¹⁰ All patients received a modified custom-made triflanged acetabular reconstruction ring, that was 3D printed with titanium powder using selective laser melting. After a minimum follow-up of 10 months, no components had to be removed and no hip had to be revised for any reason, no dislocations of the operated hip occurred and no evidence of infection was registered. Chen et al. described a 62-year-old patient who suffered from pelvic sarcoma.¹⁹ After tumour resection, a 3D printed customized implant (titanium alloy powder) was installed. The postoperative follow-up reported that all resection margins were sarcoma-free, and the status of the patient recovery was satisfactory. Wei et al. described a 62-year-old patient who underwent total *en bloc* sacrectomy because of recurrent sacral chordoma.²⁰ A 3D printed sacral prosthesis was developed with titanium alloy using EBM. At 8 months after surgery, the X-ray showed two fractured screws in bilateral ilia, while the CT showed some new bone formation around the prosthesis-ilium interface. The patient remained asymptomatic. At 1-year follow-up, patient was disease free and could walk indoor and outdoor over short distances with crutches. He did not feel any pain or spinopelvic instability. Delport et al. described a 50-year-old female with a pseudotumour after resurfacing arthroplasty for osteoarthritis of the left hip joint and a failed revision after 1 year.[Delport 2012] A triflanged custom acetabular implant was developed with titanium using Selective Laser Melting techniques. However, outcomes were not discussed in this case report.



5.3.2.11. *Spine*

Xu et al. reported a case report of a 12-year-old boy who underwent a staged spondylectomy for a C2 Ewing sarcoma.²³ A customized artificial vertebral body fabricated according to a computer model using titanium alloy powder was inserted to replace the defect between C1 and C3. The patient had an uneventful recovery and began to ambulate on postoperative day 7. Adjuvant treatment commenced 3 weeks after the surgery. He was tumour-free at the 1-year follow-up. Computed tomography studies revealed evidence of implant osseointegration and no subsidence or displacement of the construct.



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