3D-Druck von maßgefertigten oder individualisierbaren Implantaten und Schnittschablonen

EUnetHTA-Report

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EUROPEAN NETWORK FOR HEALTH TECHNOLOGY ASSESSMENT

Ludwig Boltzmann Institut
Health Technology Assessment

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Wien, Juli 2019

Zusammenfassung

Einleitung

Beschreibung der Technologie und der Komparatoren

Der vorliegende EUnetHTA Bericht bewertet 3D-gedruckte, maßgefertigte oder individualisierbare Implantate und Schnittschablonen, die bei erwachsenen PatientInnen (>18 Jahre) bei Knie-, Maxillofazial (Mund, Kiefer, Gesicht)- oder Schädelchirurgie verwendet werden können. Vom 3D-Druck wird erwartet, dass individualisierbare und personalisierte Implantate und Schnittschablonen, die von 3D-Druckgeräten hergestellt wurden, eine bessere Wirksamkeit, Sicherheit und Leistungsfähigkeit haben.

Population:
PatientInnen (>18 Jahre) mit einer Knie-, Maxillofazial (Mund, Kiefer, Gesicht)- oder Schädeloperation

Definitionen unterschiedlicher 3D-Produkte:

- *Maßgefertigtes Medizinprodukt* („custom-made medical device“): jedes Produkt, das speziell basierend auf der Verordnung eines/r qualifizierten Arztes/Ärztin hergestellt wird und das unter seiner/ihrer Verantwortung spezifische Konstruktionsmerkmale aufweist und für die alleinige Verwendung durch eine/n bestimmte/n PatientIn bestimmt ist.

- *Individualisierbares Medizinprodukt* („customisable medical device“): Medizinprodukte, die Standardprodukte sind und individuell an die Eigenschaften eines/r bestimmten PatientIn angepasst werden.
- *Schnittschablone* („cutting guide/surgical guide“): eine Schnittschablone ist ein kleines, individuelles Werkzeug aus einem sterilisierbaren Material, das kurzfristig bei einem/r PatientIn eingesetzt werden kann und die Säge und/oder den Bohrer in die geplante Richtung führt.

Intervention:
3D-gedruckte, maßgefertigte oder individualisierbare Implantate und Schnittschablonen

Als Komparatoren dienen standardmäßige, nicht 3D-gedruckte Implantate oder Schnittschablonen. Da der 3D-Druck die Möglichkeit bietet, komplexe klinische Fälle zu behandeln, für die es aufgrund ihrer Komplexität keine alternativen Behandlungsmöglichkeiten gibt, wurde auch "keine Behandlung" oder „übliche Versorgung (Standard of Care)“ als Komparator gewählt.

Komparatoren:
standardmäßige, nicht 3D-gedruckte Implantate oder Schnittschablonen

Gesundheitsproblem

3D-gedruckte Medizinprodukte werden derzeit am häufigsten in der Knie-, Maxillofazial- und Schädelchirurgie eingesetzt. Die häufigsten Krankheiten, die in den eingeschlossenen Studien dargestellt wurden, sind:

häufigste Krankheiten:

- Knie-Arthrose und sekundäre rheumatoide Arthritis, die mit totaler Kniearthroplastik (TKA) behandelt werden,
- Mundkrebs, der durch Unterkieferrekonstruktion behandelt wird,
- Traumatische Hirnverletzungen mit intrakranieller Hypertonie, die mit dekompressiver Kraniektomie und später mit Schädelplastik behandelt werden.

Knie-Arthrose und sekundäre rheumatoide Arthritis,

Mundkrebs,

traumatische Hirnverletzungen mit intrakranieller Hypertonie

Derzeit werden 3D-Drucktechnologien in Europa in nur ca. 1,3% von 1.324.000 jährlichen TKAs eingesetzt. Darüberhinaus liegen zurzeit keine publizierten Daten über den Einsatz von 3D-Drucktechnologien bei der Unterkieferrekonstruktion und der Schädelplastik in Europa vor, aber es wird angenommen, dass ihr Einsatz in diesen klinischen Bereichen zunimmt.

Methoden

systematische Literatursuche, Involvierung von klinischen und technischen ExpertInnen, EUnetHTA Dossiers von relevanten Herstellern und Internet Recherchen

Für die Bewertung der klinischen Wirksamkeit wurde eine systematische Literatursuche durchgeführt und die Studien gemäß der in diesem Bericht beschriebenen Ein- und Ausschlusskriterien ausgewählt. Die Suche erfolgte in zwei Schritten: zunächst wurde eine Suche nach systematischen Reviews (SRs) mit einer zeitlichen Beschränkung von fünf Jahren (April 2013-2018) durchgeführt. Des Weiteren wurde eine Suche nach Primärstudien (kontrollierte klinische Studien, randomisierte kontrollierte Studien (RCTs) und Beobachtungsstudien) mit einer zeitlichen Beschränkung von zehn Jahren (April 2008-2018) vorgenommen. Für die Beschreibung der Technologie und des Gesundheitsproblems sowie der Sicherheit der Technologie wurden Informationen von der systematischen Literatursuche, klinischen und technischen ExpertInnen, aus EUnetHTA Dossiers von relevanten Herstellern und Internet-Recherchen zu diesem Thema herangezogen. Die Literaturauswahl und Datenextraktion wurde von zwei ForscherInnen unabhängig voneinander durchgeführt.

- Die Qualität der eingeschlossenen SRs wurde mit dem „Risk of Bias in Systematic Reviews (ROBIS)“ Tool bewertet. — ROBIS Tool
- Das „Cochrane Risk of Bias“ (RoB2) Tool wurde verwendet, um die Qualität der eingeschlossenen RCTs zu bewerten. — Cochrane Risk of Bias Tool
- Das Bias-Risiko bei Kohorten- und Fallkontrollstudien wurde anhand von Checklisten zur Methodik vom „Scottish Intercollegiate Guidelines Network (SIGN)“ bewertet. — Checklisten von SIGN
- Für die Bewertung der Qualität der Evidenz wurde GRADE („Grading of Recommendations, Assessment, Development and Evaluation“) verwendet. — GRADE

klinische Wirksamkeit: Metaanalyse (RevMan)

Auch die Qualitätsbewertung wurde von zwei ForscherInnen unabhängig voneinander durchgeführt. Wo es möglich war, wurden für die Bewertung der klinischen Wirksamkeit Berechnungen mittels einer Metaanalyse im Review Manager (RevMan Version 5.3, The Cochrane Collaboration) durchgeführt.

Ergebnisse

primäre und sekundäre Endpunkte für Kniearthroplastik, Maxillofazial-Chirurgie, Schädelchirurgie

Die Endpunkte hinsichtlich klinischer Wirksamkeit und Sicherheit in diesem Bericht waren:

Endpunkte für PatientInnen, die sich einer Kniearthroplastik unterzogen:
Primäre Endpunkte:

- “Patient Reported Outcome Measures (PROMs)”:
  - Schmerzen gemessen mit dem „Visual Analogue Scale (VAS)“ oder „Numerical Pain Ranking Scale (NPRS)“
  - Gesundheitsbezogene Lebensqualität (QoL) - (generisch oder krankheitsspezifisch)
  - PatientInnenzufriedenheit
- Postoperative Funktion/Leistung, gemessen durch validierte Tests, d.h. „Timed-Up-and-Go-Test“, Treppensteige-Test („Stair Climb Test“) oder 6-minütiger Gehtest.
- Funktion gemessen durch validierte klinische Ergebniswerte, d.h. Knieverletzung und Osteoarthritis Outcome Score oder Funktionsskala der unteren Extremitäten.

Sekundäre Endpunkte:

- Operationszeit (in Bezug auf die Risikominimierung von Infektionen, Ischämie und Blutverlust)

- Gesamte Ausrichtung/Position („alignment“) der Extremitäten (von funktioneller Relevanz)
- Strapazierfähigkeit des Produktes
- Langlebigkeit des Produktes
- Unerwünschte Ereignisse

primäre und sekundäre Endpunkte für Maxillofazial-Chirurgie

Endpunkte für PatientInnen, die sich einer Maxillofazial-Chirurgie unterzogen:
Primäre Endpunkte:

- “Patient Reported Outcome Measures (PROMs)”:
    - Die Mundgesundheit gemessen auf validierten spezifischen Ergebnisskalen, z.B. dem „Oral Health Impact Profile (OHIP-14)“ oder der „United Kingdom Oral Health-Related Quality of Life Measure“ (OHQoL-UK).
    - Gesundheitsbezogene Lebensqualität (QoL) - (generisch oder krankheitsspezifisch)
    - Schmerzen gemessen mit VAS oder NPRS
    - PatientInnenzufriedenheit

Sekundäre Endpunkte:
- Operationszeit (in Bezug auf die Risikominimierung von Infektionen, Ischämie und Blutverlust)
- Menge der Knochenentnahme („bone harvest“) während der Operation
- Strapazierfähigkeit des Produktes
- Langlebigkeit des Produktes
- Unerwünschte Ereignisse

primäre und sekundäre Endpunkte für Schädelchirurgie

Endpunkte für PatientInnen, die sich einer Schädelchirurgie unterzogen:
Primäre Endpunkte:

- “Patient Reported Outcome Measures (PROMs)”:
    - Gesundheitsbezogene Lebensqualität (QoL) - (generisch oder krankheitsspezifisch)
    - Schmerzen gemessen mit VAS oder NPRS
- Präzision/Genauigkeit (von kosmetischer/ästhetischer und funktioneller Relevanz)
- PatientInnenzufriedenheit

Sekundäre Endpunkte:
- Operationszeit (in Bezug auf die Risikominimierung von Infektionen, Ischämie und Blutverlust)
- Strapazierfähigkeit des Produktes
- Langlebigkeit des Produktes
- Unerwünschte Ereignisse

Verfügbare Evidenz

Dreizehn Studien erfüllten die Einschlusskriterien: sechs RCTs und zwei SRs berichteten über PatientInnen, die sich einer Knierekonstruktion unterzogen hatten; drei RCTs und eine prospektive Studie involvierten PatientInnen bei denen eine Operation im Maxillofazialbereich durchgeführt wurde (insbesondere PatientInnen mit einer Unterkieferrekonstruktion); und eine prospektive Studie untersuchte PatientInnen mit einer Schädelplastik.

klinische Wirksamkeit: 13 Studien eingeschlossen (2 SRs, 9 RCTs, 2 prospektive Studien)

Sechs Studien wurden in die quantitative Metaanalyse miteinbezogen. Alle Studien zur klinischen Wirksamkeit wurden auch für Aussagen zur Sicherheit eingeschlossen, ebenso wie drei weitere Studien, welche über Sicherheitsbedenken in der Maxillofazial- und Schädelchirurgie berichteten.

Sicherheit: plus 3 Studien

quantitative Metaanalyse: 6 Studien eingeschlossen

Klinische Wirksamkeit

Insgesamt war das Evidenzniveau der eingeschlossenen Studien sehr niedrig bis moderat, was hauptsächlich auf das Bias-Risiko und die geringe Präzision der Effektschätzer (weite Konfidenzintervalle) in den eingeschlossenen Studien zurückzuführen ist. Die sehr niedrige oder niedrige Qualität der Evidenz zeigte, dass

- die 3D-Operation mit 3D-Druckimplantaten und Schnittschablonen in der TKA im Vergleich zu Standardimplantaten und Schnittschablonen präziser war, wie durch die Endpunkte Fehlstellung (Hüft-Knie-Schenkel-Winkel, koronale Oberschenkel-Ausrichtung und koronale Schienbein-Ausrichtung) oder absolute Abweichungen gezeigt wurde.
- darüberhinaus keine weiteren klinisch relevanten oder signifikanten Ergebnisse oder Endpunkte zugunsten der 3D-Drucktechnologie oder der Standardoperation für die anderen Indikationen berichtet wurden.

Solange keine qualitativ hochwertigere Evidenz vorliegt, kann keine endgültige Entscheidung über den weiteren Einsatz der 3D-Drucktechnologie getroffen werden. Es sind weitere Evaluierungen der 3D-Technologien und Operationen notwendig.

Evidenzniveau der eingeschlossenen Studien sehr niedrig bis moderat

3D-Druckimplantate und Schnittschablonen in der TKA im Vergleich zu Standardimplantate und Schnittschablonen präziser

keine weiteren klinisch relevanten oder signifikanten Endpunkte zugunsten der 3D-Drucktechnologie oder der Standardoperation

Sicherheit

Die Sicherheit der 3D-gedruckten Implantate und Schnittschablonen wurde in einigen der eingeschlossenen Studien im Vergleich zu Standardimplantaten und Schnittschablonen untersucht. Es wurden keine Unterschiede bei den Komplikationen der Technologien zur TKA, Unterkieferrekonstruktion und Schädelplastik berichtet, wohingegen ein Unterschied in der ischämischen Zeit bei der Unterkieferrekonstruktion beobachtet wurde: die ischämische Zeit war in der Gruppe mit individuellen, 3D-gedruckten, chirurgischen Schablonen im Vergleich zur Standardrekonstruktionsgruppe kürzer.

keine Unterschiede bei den Komplikationen der Technologien zur TKA, Unterkiefer-rekonstruktion und Schädelplastik, Unterschied in der ischämischen Zeit bei der Unterkiefer-rekonstruktion

Die Daten in diesen Studien beschrieben allerdings nur die kurzfristigen Endpunkte wie Infektion, venöse Thromboembolien, Hämarthrose, Ischämie und Operationszeit. Keine Aussagen können zu langfristigen Sicherheitsendpunkten gemacht werden.

Organisatorische und rechtliche Aspekte

Organisatorische Veränderungen

Änderungen im Arbeitsablauf und in den Kompetenzen des Personals

Organisatorische Veränderungen sind unvermeidlich, wenn 3D-gedruckte Implantate und Schnittschablonen als Ergänzung oder Ersatz für Standard-Implantate und Schnittschablonen eingesetzt werden. Diese Veränderungen bestehen im Wesentlichen aus Änderungen im Arbeitsablauf in der Krankenhausabteilung sowie aus Änderungen in den Kompetenzen des Personals. Die Auswirkungen dieser Veränderungen hängen vom implementierten Organisationsszenario ab.

Anforderungen an den Marktzugang

individualisierbare Medizinprodukte in der Regel als maßgefertigte Produkte klassifiziert: bisher keine CE-Kennzeichnung für maßgefertigte Produkte notwendig

Derzeit gelten individualisierbare Medizinprodukte als verschreibungspflichtige Produkte, die für den/die einzelne/n PatientIn hergestellt werden, auch wenn sie manchmal das Potenzial haben, in Serie hergestellt zu werden. Daher werden sie in der Regel im Hinblick auf den Marktzugang als maßgefertigte Produkte klassifiziert. Im Gegensatz zu "Standard"-Medizinprodukten benötigen Hersteller von maßgefertigten Produkten, unabhängig vom Risikoprofil und gemäß der Medizinprodukteverordnung, keine CE-Kennzeichnung für ihr Produkt.

Haftung

Haftungsprinzip für 3D-Druckimplantate und Schnittschablonen anwendbar - gilt nicht für den Fall der Großserienproduktion

Regelungslücken

Nach den Grundsätzen der Produkthaftung, haftet der Hersteller für jeden Mangel an seinem Produkt. Der 3D-Druck weicht von der traditionellen Kette aus Produktion, Vertrieb und Nutzung ab. Einerseits ist der Hersteller schwer zu identifizieren, da in den meisten Fällen viele Parteien an der Herstellung von 3D-Druckgeräten beteiligt sind. Andererseits ist die Gesetzeslage von maßgefertigten oder individualisierbaren 3D-Druckimplantaten und Schnittschablonen aufgrund von Regelungslücken unklar. Bei 3D-Druckern ist die Großserienproduktion eine Option, aber die aktuelle Verordnung berücksichtigt diese Möglichkeit nicht. Obwohl das Haftungsprinzip für 3D-Druckimplantate und Schnittschablonen anwendbar ist, gilt dies nicht für den Fall der Großserienproduktion.

Schutz personenbezogener Daten

Verarbeitung der Gesundheitsdaten notwendig

Das 3D-Druckverfahren beinhaltet zwangsläufig auch die Verarbeitung der Gesundheitsdaten der/des einzelnen PatientIn. Das Datenschutzgesetz schützt die Verarbeitung personenbezogener Daten und enthält entsprechende Regeln. Es ist wichtig zu wissen, wer von der/dem GesetzgeberIn als „für die Verarbeitung verantwortliche Person" angesehen wird.

Laufende Studien

3 laufende Studien (2 RCTs und 1 Interventionsstudie)

Derzeit laufen drei Studien: ein RCT zur Untersuchung maßgefertigter Modelle für das Biegen von Gesichtsschädel-Implantaten (Rekrutierung noch nicht begonnen), ein RCT zur Überprüfung personalisierter Oberkieferfixationsplatten (Rekrutierung im Gange) und eine Interventionsstudie ohne Randomisierung, welche die Verwendung von patientenspezifischen Titanplatten für die Kieferchirurgie testet (Rekrutierung noch nicht begonnen).

Diskussion

Diese Bewertung vergleicht die 3D-Operation mit 3D-gedruckten Implantaten und Schnittschablonen mit der entsprechenden Standardoperation in den drei Bereichen: Knie-, Maxillofazial- und Schädelchirurgie. Die Analyse zeigte eine signifikant höhere Präzision bei der 3D-Operation im Vergleich zur Standardoperation bei TKA, gemessen an den Endpunkten Fehlstellungen oder absolute Abweichungen. Die Qualität der Evidenz war jedoch sehr gering bis moderat. Diese Ergebnisse sind statistisch signifikant in Bezug auf das Ausmaß der Veränderung. Darüberhinaus liegen keine weiteren statistisch signifikanten Ergebnisse zugunsten einer 3D- oder Standardoperation bei anderen Endpunkten oder anderen Indikationen.

Evidenz: sehr gering bis moderat

signifikant höhere Präzision bei der 3D-Operation im Vergleich zur Standardoperation bei TKA

keine weiteren statistisch oder klinisch signifikanten Ergebnisse zugunsten einer 3D- oder Standardoperation

Relevante Endpunkte (Ausrichtung) sind Proxy-Endpunkte und lassen keine Aussagen auf eine zukünftige, direkte Auswirkung auf die/den PatientIn zu, wie z.B. verminderte Schmerzen oder erhöhte Lebensqualität (QoL). Zukünftige Studien müssen einen eindeutigen Zusammenhang zwischen Fehlstellungen und langfristigen patientenrelevanten Endpunkten herstellen, und Methoden zur Messung der Ausrichtung müssen weiter validiert werden. Obwohl es keine Unterschiede in den Komplikationen zwischen den Technologien beobachtet wurden, müssen langfristige Komplikationen wie Implantatversagen, Prothesenprobleme und anhaltende Schmerzen weiter und umfassend evaluiert werden, um festzustellen, welche Sicherheitsprobleme durch die Einführung dieser neuen Technologie auftreten können.

langfristige Komplikationen sollen weiter evaluiert werden

Die wichtigste rechtliche Frage im Zusammenhang mit der 3D-Drucktechnologie ist, ob die individualisierbaren Medizinprodukte mit einer CE-Kennzeichnung versehen werden müssen oder nicht. Neue EU-Verordnungen verschärfen die Anforderungen an 3D-gedruckte Medizinprodukte, die in größeren Stückzahlen hergestellt werden, aber in vielen Fällen gelten individualisierbare Produkte als individuelle, maßgefertigte Produkte und unterliegen daher nicht einer CE-Kennzeichnung, obwohl sie oft in Standardproduktionsprozessen hergestellt werden. Dies bedeutet, dass individualisierbare Medizinprodukte möglicherweise die gleichen Bedingungen für den Marktzugang erfüllen müssten wie Standard-Medizinprodukte. Trotz der neuen Verordnungen (MDR/ IVDR) bestehen derzeit (und in Zukunft) unterschiedliche gesetzliche Anforderungen für die verschiedenen Arten der 3D-gedruckten Medizinprodukte sowie für die 3D-gedruckten Medizinprodukten im Vergleich zu deren Komparatoren (Standard-Medizinprodukten).

neue EU Verordnungen legen gesetzliche Anforderungen fest

Die Herausforderung bei der Identifizierung der Verantwortlichen für die 3D-Druckgeräte bleibt bestehen, da sich der Hersteller des 3D-Druckers und der Hersteller der Produkte in den meisten Fällen unterscheiden, obwohl die Haftung nach geltendem Recht klar ist und für alle Beteiligten gilt.

Hersteller des 3D-Druckers und der Produkte in den meisten Fällen unterschiedlich:

wirft Haftungsfragen auf

Schlussfolgerung

Die sehr niedrige bis niedrige Qualität der Evidenz zeigt signifikante Unterschiede in der Präzision in Bezug auf Fehlausrichtung und Abweichung zwischen der 3D-Drucktechnologie und der Standardinstrumente in der TKA. Um diese signifikanten Ergebnisse zu validieren und endgültige Schlussfolgerungen ziehen zu können, ist eine Evidenz von höherer Qualität erforderlich. Bei der Unterkieferrekonstruktion und der Schädelplastik lassen sich keine eindeutigen Schlussfolgerungen ziehen, da es keine signifikanten Endpunkte zugunsten einer von beiden Technologien gab. Was die Sicherheit betrifft, so wurde zwar über einige kurzfristige Endpunkte wie Infektion, venöse Thromboembolien und Hämarthrose berichtet, aber es wurden keine Unterschiede abseits der ischämischen Zeit bei der Unterkieferrekonstruktion zwischen den untersuchten Technologien beobachtet.

Evidenz von höherer Qualität erforderlich, um Schlussfolgerungen zu ziehen

EUnetHTA Joint Action 3 WP4

Rapid assessment of other technologies using the HTA Core Model® for Rapid Relative Effectiveness Assessment

Custom-made or customisable 3D printed implants and cutting guides versus non-3D printed standard implants and cutting guides for improving outcome in patients undergoing knee, maxillofacial, or cranial surgery

PROJECT ID: OTCA11

Version 1.4, 17th April 2019

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Disclaimer

The assessment represents a consolidated view of the EUnetHTA assessment team members and is in no case the official opinion of the participating institutions or individuals.

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Conflicts of interest

All authors, co-authors, dedicated reviewers and external experts involved in the production of this assessment have declared they have no conflicts of interest in relation to the technology and comparator assessed according to the EUnetHTA Declaration of Interest and Confidentiality Undertaking (DOICU) statement except one external expert, Professor Constantinus Politis. He declares a financial or another relationship with a Developing and/or Producing and/or Distributing Organisation (DPDO) for the technology or comparators undergoing assessment, and thus has a conflict of interest according to the EUnetHTA guidelines for handling conflicts of interest. Professor Constantinus Politis acted as Head and Chair of a research group working on development and validation of surgical tools and image-based solutions in oromaxillofacial surgery. Among others, KLS Martin funds this research group. There is no single contract between professor Constantinus Polits and KLS Martin, and there is no commercial relationship between the surgical department and KLS Martin. He has no other conflicts of interest related to the topic of 3D printed custom-made and customisable implants and surgical guides. According to the EUnetHTA guidelines for handling conflicts of interest, the involvement of Professor Constantinus Polits as an external expert is acceptable for commenting on the draft assessment.

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LIST OF ABBREVIATIONS

ABS	Acrylonitrile butadiene styrene
AM	Additive manufacturing
CAD	Computer-aided design
CDSR	Cochrane Database of Systematic Reviews
CI	Confidence interval
CT	Computed tomography
CUR	Current use of the technology
DARE	The Database of Abstracts of Reviews of Effects
DC	Decompressive craniectomy
DLF	Direct laser forming
DMLS	Direct metal laser sintering
DOICU	Declaration of interest and confidentiality undertaking
EBM	Electron beam melting
EDP	Environmentally degradable polymer
EFF	Clinical effectiveness
ETH	Ethical
EULAR	European League Against Rheumatism
EUnetHTA	European Network for Health Technology Assessment
FDA	Food and Drug Administration
FDM	Fused deposition modelling
GCS	Glasgow coma scale
GRADE	Grading of Recommendations, Assessments, Development and Evaluation
HA-reinforced	Hydroxyapatite reinforced
HDPE	High-density polyethylene
HIPS	High-impact polystyrene
HRQoL	Health-related quality of life
ICD	International Classification of Diseases
ICH	Intracranial hypertension
ICU	Intensive care unit
KSS	Knee Society Score
LEG	Legal
MeSH	Medical Subject Headings
MJM	Multi-jet modelling
NRS	Non-randomised studies
NT	Navigation template
OA	Osteoarthritis
OHIP	Oral Health Impact Profile
ORG	Organisational
OSCC	Oral squamous cell carcinoma

P[PF-co-EG]	Poly(propylene fumarate-co-ethylene glycol)
P(AN-co-allyl sulfonate)	Poly(acrylonitrile-co-allyl sulfonate)
P(GEMA- sulfate)	Poly(glucosyloxyethyl methacrylate) sulfate
P(MMA-co-HEMA)	Poly(methyl methacrylate-co-2-hydroxyethyl methacrylate)
P(NIPAAm-co-AAc)	Poly(N-isopropylacrylamide-co-acrylic acid)
P(NIPAAm-co-EMA)	Poly (N-isopropyl acrylamide-co-ethyl methacrylate)
PAAm	Polyacrylamide
PBO	Polybutylene oxide
PC	Polycarbonate
PCL	Polycaprolactone
PEEK	Polyether ether ketone
PEG	Polyethylene glycol
PEG±CDs	Polyethylene glycol-modified carbonaceous dots
PEG-g-P(AAm-co-vamine)	Polyethylene glycol-grafted-polyacrylamide-co-vamine
PES	Polyester
PHB	Polyhydroxybutyrate
PICO	Patient-Intervention-Comparison-Outcome
PLA	Polylactic acid
PLGA	Poly(lactic acid-co-glycolic acid)
PLLA	Poly-L-lactic acid
PMMA	Poly(methyl methacrylate)
PMPGs	Patient-matched positioning guides
PNVP	Poly(N-vinylpyrrolidone)
PP	Polypropylene
PPSF	Polyphenylsulfone
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-analyses
PS	Polystyrene
PSI	Patient-specific instruments
PTFE	Polytetrafluoroethylene
PVA	Poly(vinyl alcohol)
PVAc	Poly(vinyl acetate)
QALYs	Quality-adjusted life years
QoL	Quality of life
RA	Rheumatoid arthritis
RCT	Randomised controlled trial
REA	Relative Effectiveness Assessment
RevMan	Review Manager
ROBIS	Risk of Bias in Systematic Reviews
RP system	Rapid prototyping system
SAF	Safety

SIGN	Scottish Intercollegiate Guidelines Network
SLA	Stereolithography
SLM	Selective laser melting
SLS	Selective laser sintering
SOC	Social
SR	Systematic review
SSRO	Sagittal split ramus osteotomy
TBI	Traumatic brain injury
TEC	Technical characteristics of the technology
TKA	Total knee arthroplasty
TIJ	Thermal inkjet printing
TNM	Tumour-node-metastasis
UHMWPE	Ultra-high molecular weight polyethylene
UV	Ultraviolet
VAS	Visual analogue scale
WOMAC	Western Ontario and McMaster Universities Osteoarthritis Index

1 SUMMARY OF RELATIVE EFFECTIVENESS OF 3D PRINTED CUSTOM-MADE OR CUSTOMISABLE IMPLANTS AND CUTTING GUIDES VERSUS NON-3D PRINTED STANDARD IMPLANTS AND CUTTING GUIDES

1.1 Scope

The scope of this assessment is 3D printed custom-made or customisable implants and cutting guides used in adult patients (>18 years) undergoing knee, maxillofacial, or cranial surgery. Comparators of interest are standard non-3D printed implants or cutting guides. 3D printing offers the opportunity to treat complex clinical cases with no alternative treatments available due to their complexity. In these cases, where no standard solutions are available, the comparison is "no treatment" or "usual care". The scope can be found here.

1.2 Introduction

Description of technology and comparators

The technology described in this assessment is the use of 3D print technology to produce custom-made or customisable 3D printed implants and cutting guides versus non-3D printed standard implants and cutting guides for improving outcomes in patients undergoing knee, maxillofacial, or cranial surgery. The claimed benefit of 3D printed devices is the production of customisable and personalised guides and implants that subsequently improve safety, performance, and effectiveness.

Health problem

3D printed medical devices are currently most frequently applied in knee, maxillofacial, and cranial surgery. The most frequent diseases represented in the included studies are knee osteoarthritis (OA) and secondary rheumatoid arthritis treated with total knee arthroplasty (TKA), oral cancer treated by mandibular reconstruction, and traumatic brain injury (TBI) with intracranial hypertension (ICH) treated with decompressive craniectomy (DC) and later cranioplasty. Each year worldwide, approximately 1% of the population contacts a doctor with symptoms of knee arthritis, oral cancer affects over 300,000 people, and TBI over 10 million people. In Europe, 3D printing technologies are currently used in only ~1.3% of 1,324,000 annual TKAs (1,2). There are currently no published data on the utilization of 3D printing technologies in mandibular reconstruction and cranioplasty in Europe, but its use is known to be increasing in these clinical areas.

1.3 Methods

A systematic literature search was performed for the effectiveness domain (EFF) of this assessment. The search met the inclusion and exclusion criteria described in the Scope of this assessment. The search was performed in two steps. First, a search for systematic reviews (SRs) was performed with a time limit of five years (April 2013-2018). Second, a search for primary studies was performed with a time limit of ten years (April 2008-2018) including controlled clinical trials, randomised controlled trials (RCTs), and observational studies. For the technical characteristics (TEC), current use (CUR), and safety (SAF) domains, information was identified through the systematic literature search, clinical and technical experts, manufacturer submission files, and internet searches on the topic. Literature selection and data extraction were performed independently by two researchers.

The quality of the included reviews was assessed using the Risk of Bias in Systematic Reviews (ROBIS) tool. The Cochrane risk-of-bias (RoB2) tool was used to assess the quality in the inclu-

ded RCTs. Risk of bias in cohort and case-control studies was assessed using Scottish Intercollegiate Guidelines Network (SIGN) methodology checklists. The quality of the body of evidence was assessed using Grading of Recommendations, Assessment, Development and Evaluations (GRADE). Quality assessment was performed independently by two researchers. For the EFF domain, statistical summary estimates of associations across studies were where possible derived through a random effects meta-analysis using Review Manager (RevMan version 5.3, The Cochrane Collaboration).

1.4 Results

The findings are summarised in Table 1.1.

Available evidence

Thirteen studies met the inclusion criteria: six RCTs and two SRs reported on patients undergoing knee reconstruction; three RCTs and one prospective study reported on maxillofacial patients (specifically, patients undergoing mandibular reconstruction); and one prospective study examined patients undergoing cranioplasty. The study characteristics are detailed in Table A.1 and Table A.2. Six studies were included in the quantitative meta-analysis. All studies from the EFF domain were included in the SAF domain together with three additional studies regarding safety concerns in maxillofacial and cranial surgery.

Clinical effectiveness

Overall, the evidence level for the included studies was very low to moderate, mainly due to the risk of bias and the imprecision of the estimates in the included studies. Therefore, the robustness of the findings may be limited. There was very low or low quality evidence showing that 3D surgery using 3D printed implants and cutting guides in TKA compared with standard instrumentation was more precise, as demonstrated through outcomes such as malalignment (hip-knee-ankle angle, coronal femoral alignment, and coronal tibial alignment) or absolute deviation. There were no other clinical relevant or significant results or outcomes in favour of 3D print technology or standard surgery. Consequently, 3D surgery requires further evaluation. Until higher quality evidence is generated, no final decision on the continued use of 3D print technology can be made.

Safety

Safety issues related to 3D printed implants and cutting guides compared with standard implants and cutting guides were examined in a few of the included studies. There was no overall difference in complications between the technologies in TKA, mandibular reconstruction, and cranioplasty. There was a difference in ischaemic time in mandibular reconstruction, with a decrease in ischaemic time in the group using individual 3D printed surgical guides compared to the standard reconstruction group. The data in these studies described only short-term outcomes such as infection, venous thromboembolism, haemarthrosis, ischaemia, and operating time.

Organisational and legal aspects

Organisational changes

Organisational changes are inevitable if 3D printed implants and surgical guides are implemented as a supplement to or as a replacement for standard implants and surgical guides. These changes will mainly consist of workflow changes in the hospital department and competency changes for personnel. The impact of these changes will depend on the organisational scenario implemented.

Requirements for market access

Currently, customisable devices are regarded as prescription devices made for individual patients, even though they sometimes have the potential to be mass produced. As a consequence, they are usually classified together with custom-made devices with respect to market access. In contrast to "standard" medical devices, manufacturers of custom-made medical devices, regardless of the risk profile and according to the Medical Device Directive, do not apply CE marking to their product.

Liability

According to the principles of product liability, the producer is liable for any defect in its product. 3D printing deviates from the traditional chain of production, distribution, and use. On the one hand, the producer is difficult to definitively identify, since in most cases many parties are involved in 3D printed device production. On the other, the legalities of custom-made or customisable 3D printed implants and cutting guides remain unclear due to regulatory gaps. Manufacturer's statements are devoted to single or short series production of medical devices. In the case of 3D printers, large-scale production is an option, but current regulation does not take this issue into account. Although the principles of liability are applicable to 3D printed implants and cutting guides, this does not cover the case of large-scale production.

Protection of person data

The 3D printing process unavoidably also involves the processing of the health data of the individual patient. Privacy legislation protects the processing of personal data and has rules for this. It is very important to know who is regarded as "responsible for processing" by law.

Upcoming evidence

Three ongoing studies are detailed in Table A.3: two RCTs investigating custom-made models for bending implants (not yet recruiting) and personalised maxillary fixation plates (recruiting), and one intervention study without randomisation investigating the use of patient-specific titanium plates for jaw surgery (not yet recruiting).

Table 1.1: Summary of findings table for 3D printed implants and cutting guides

Outcome	Anticipated absolute effects (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Quality
	Risk with comparison	Risk with 3D print technology			
Proportion of outliers (>3°) - hip-knee-ankle alignment	303 per 1.000	112 per 1.000 (65 to 185)	OR 0.29 (CI 0.16-0.52)	319 (4 RCTs)	⊕⊕◯◯ LOW
Absolute deviation in degrees	-	The mean absolute deviation in degrees in the intervention group was 1.28 degrees lower (3.29 lower to 0.74 higher)	-	159 (2 RCTs)	⊕◯◯◯ VERY LOW
Operating time	-	The mean operating time in the intervention group was 9.47 minutes lower (18.1 lower to 0.84 lower)	-	239 (3 RCTs)	⊕⊕◯◯ LOW
Oxford knee score (OKS) (1-year follow-up)	-	The mean OKS (1-year follow-up) in the intervention group was 1.29 points higher (0.84 lower to 3.41 higher)	-	289 (2 RCTs)	⊕⊕⊕◯ MODERATE
Knee Society function score (3-months follow-up)	-	The mean Knee Society function score (3-months follow-up) in the intervention group was 0 (0 to 0)	-	240 (2 RCTs)	⊕⊕◯◯ LOW
Proportion of outliers (>3°) - coronal femur	214 per 1.000	61 per 1.000 (24 to 156)	OR 0.24 (CI 0.09- 0.68)	319 (4 RCTs)	⊕⊕◯◯ LOW
Proportion of outliers (>3°) - coronal tibia	172 per 1.000	57 per 1.000 (24 to 126)	OR 0.29 (CI 0.12-0.69)	319 (4 RCTs)	⊕⊕◯◯ LOW
Proportion of outliers (>3°) - tibial slope	209 per 1.000	194 per 1.000 (117 to 305)	OR 0.91 (CI 0.50-1.66)	249 (3 RCTs)	⊕◯◯◯ VERY LOW

1.5 Discussion

This assessment compared 3D surgery using 3D printed implants and cutting guides and standard surgery in three areas: knee, maxillofacial, and cranial surgery. The analysis showed significantly greater precision with 3D surgery compared to standard surgery in TKA as demonstrated through outcomes such as malalignment or absolute deviation. However, the quality of evidence was only very low to moderate. These results are both statistically significant and also clinically significant in relation to the magnitude of change. There were no other statistically nor clinically significant results in favour of 3D or standard surgery. Relevant outcomes (alignment) are proxy outcomes, and do not necessarily indicate a future direct effect on the patient such as increased pain or decreased quality of life (QoL). Future studies need to establish a firm association between malalignment and long-term patient-relevant outcomes, and methods used to measure alignment need further validation. Although there were no overall differences in complications between the technologies, long-term complications such as implant failure, prosthesis problems, and continued pain need further, more extensive evaluation in order to recognize which safety issues this new technology could introduce.

The main legal issues regarding 3D printed technology concern whether or not customisable devices must be CE marked. New EU regulations impose stricter requirements for 3D printed medical devices made in larger quantities, but in many cases customisable devices are considered individual custom-made devices and therefore do not need to bear the CE mark even though they are often produced using standard production processes. This means that customisable medical devices may need to comply with the same conditions as standard medical devices for market access. Despite these new regulations, current (and future) different legal requirements exist between the different types of 3D printed medical devices and between 3D printed medical devices and the comparators (standard medical devices). Challenges remain in identifying who is responsible for 3D printed devices, as the manufacturer of the 3D printer and the devices differ in most cases, notwithstanding that the liability under current law is clear and applies to all involved parties.

1.6 Conclusion

Evidence of very low or low quality shows significant differences in precision in terms of malalignment and deviation between 3D printed technology and standard instrumentation in TKA. Evidence of higher quality is needed to validate these significant results and draw final conclusions. No firm conclusions can be made in mandibular reconstruction and cranioplasty, since no outcomes were significant in favour of either technology. Regarding safety, while a few short-term outcomes such as infection, venous thromboembolism, and haemarthrosis were reported, there were no overall differences except from ischaemic time in mandibular reconstruction between the assessed technologies.

2 SCOPE

Table 2.1: Scope according to population, intervention, comparison, outcomes, and study design analysis

Description	Project Scope
Population	Adult patients (>18 years) undergoing knee, maxillofacial, or cranial surgery.
Intervention	The intervention under assessment is 3D printed custom-made or customisable implants and cutting guides used in patients undergoing knee, maxillofacial, or cranial surgery (for product names see Table 4.3). The following MeSH terms are applied: Printing, Three-Dimensional; Stereolithography; Computer-Aided Design.
Comparison	Comparators of interest are standard non-3D printed implants or cutting guides. In some cases, 3D printing offers the opportunity to treat complex cases that have no alternative treatment due to complexity. In these cases, where no standard solutions are available, the comparison will be "no treatment" or "usual care".

Outcomes	**Outcomes for patients undergoing knee arthroplasty**
	Primary outcomes of interest:
	• Patient Reported Outcome Measures (PROMs):
	  ○ Pain measured by the Visual Analogue Scale (VAS) or Numerical Pain Ranking Scale (NPRS)
	  ○ Health-related QoL (generic or disease-specific)
	  ○ Patient satisfaction
	• Post-operative function/performance measured by validated tests, i.e., Timed-Up-and-Go Test, Stair Climb Test, or 6-Minute Walk Test.
	• Function measured by validated clinical outcome scores, i.e., Knee injury and Osteoarthritis Outcome Score or Lower Extremity Functional Scale
	Secondary outcomes of interest:
	• Operation time (in relation to minimising risk of infection, ischaemia, and blood loss)
	• Overall limb alignment (of functional relevance)
	• Durability of the device
	• Longevity of the device
	• Adverse events

	Outcomes for patients undergoing maxillofacial surgery
	Primary outcomes of interest:
	• PROMs:
	  ○ Oral health measured by validated specific outcome scales, i.e., Oral Health Impact Profile (OHIP-14) or the United Kingdom Oral Health-Related Quality of Life measure (OHQoL-UK)
	  ○ Health-related QoL (generic or disease-specific)
	  ○ Pain measured by VAS or NPRS
	  ○ Patient satisfaction

Description	Project Scope
	Secondary outcomes of interest: • Operating time (in relation to minimising risk of infection, ischaemia, and blood loss) • Amount of bone harvest used in surgery • Durability of the device • Longevity of the device • Adverse events

	Outcomes for patients undergoing cranial surgery
	Primary outcomes of interest:
	• PROMs:
	  ○ Health-related QoL (generic or disease-specific)
	  ○ Pain measured by VAS or NPRS
	• Precision/accuracy (of cosmetic/aesthetic and functional relevance)
	• Patient satisfaction
	
	Secondary outcomes of interest:
	• Operating time (in relation to minimising risk of infection, ischaemia and blood loss)
	• Durability of the device
	• Longevity of the device
	• Adverse events

Study design	For the EFF and SAF domains, the following study types were eligible for inclusion: • High-quality SRs or meta-analyses of RCTs or controlled trials published with the last 5 years and RCTs or controlled trials published with the last 10 years • If the subject under assessment does not allow the possibility of an RCT or other controlled trial (e.g., the comparator is "no treatment"), evidence of lower quality was included in the assessment • Studies that compared different types of 3D printed implants or cutting guides were excluded. Studies addressing 3D printing of products incorporating biomaterials like drugs, xenogenic cell therapy preparations, 3D printed drugs, or 3D bioprinting (3D fabrication technology involving biological tissues, organs, and cells for medical and biotechnology applications) were also excluded For the TEC and CUR domains, the completed EUnetHTA submission files from the manufacturers were used as a starting point. Furthermore, information for these domains was obtained from external experts with knowledge of the technology and literature (i.e., descriptive publications), the grey literature, and anecdotal information from general internet searches. Potential social, ethical, legal, and organisational aspects were identified through clinical experts and legal documents.

3 METHODS AND EVIDENCE INCLUDED

3.1 Assessment Team

Description of the distribution of the work between Authors and Co-authors:

DEFACTUM - Social & Health Services and Labour Market (DEFACTUM) (Author):

- Developed the first draft of the EUnetHTA project plan and amended the draft as necessary
- Performed the literature search
- Carried out the assessment of the health problem and current use of the technology (CUR), clinical effectiveness (EFF) and safety (SAF) domains
- Completed the checklist regarding potential "Ethical, organisational, patient and social, and legal aspects" of the HTA Core Model® for rapid REAs
- Sent "draft versions" to reviewers and compiled feedback from reviewers and performed changes according to reviewers' comments on the CUR, EFF, and SAF domains
- Prepared the final assessment and wrote a final summary of the assessment

Basque Office for Health Technology Assessment (OSTEBA) (Co-author):

- Reviewed draft of EUnetHTA project plan. Checked and approved all steps (e.g., literature selection, data extraction, assessment of risk of bias)
- Carried out the assessment of the TEC domain and performed changes according to reviewers' comments on the TEC domain
- Reviewed draft assessment, proposed amendments where necessary, and provided feedback on: information retrieval; sources and search terms for locating domain-specific information; and inclusion/exclusion criteria for studies or other information in terms of content, methods and quality

3.2 Source of assessment elements

The selection of assessment elements was based on the HTA Core Model4® Application for Rapid Relative Effectiveness Assessments (REA) (4.2). The assessment elements were translated to research questions that would be addressed in the assessment. Additionally, assessment elements from other HTA Core Model® Applications (for medical and surgical interventions, diagnostic technologies, or screening) were screened and included/merged with the existing questions if deemed relevant. Furthermore, the checklist for potential ethical, organisational, patient and social, and legal aspects of the HTA Core Model® for rapid REA was completed.

3.3 Search

A systematic literature search was performed for the effectiveness domain (EFF) of this assessment. The search was performed to meet the inclusion and exclusion criteria described in the Scope of this assessment. The search was performed in two steps. First, a search for SRs was performed with a time limit of five years (April 2013-2018). Second, a search for primary studies was performed with a time limit of ten years (April 2008-2018) including controlled clinical trials, RCTs, and observational studies. No language restrictions were used in any of the searches.

The search strategy is detailed in Appendix 1.

The following sources of information were used in the search:

- The Cochrane Library (including The Cochrane Database of Systematic Reviews (CDSR), The Database of Reviews of Effects (DARE), The Cochrane Central Register of Controlled Trials, and The Cochrane Methodology Register)
- EMBASE
- PubMed
- Manual searches (in the reference lists of relevant studies)

In addition, the following clinical trial databases were searched to identify on-going studies on custom-made or customisable 3D printed implants and/or cutting guides:

- ClinicalTrials.gov
- EU Clinical Trials Register

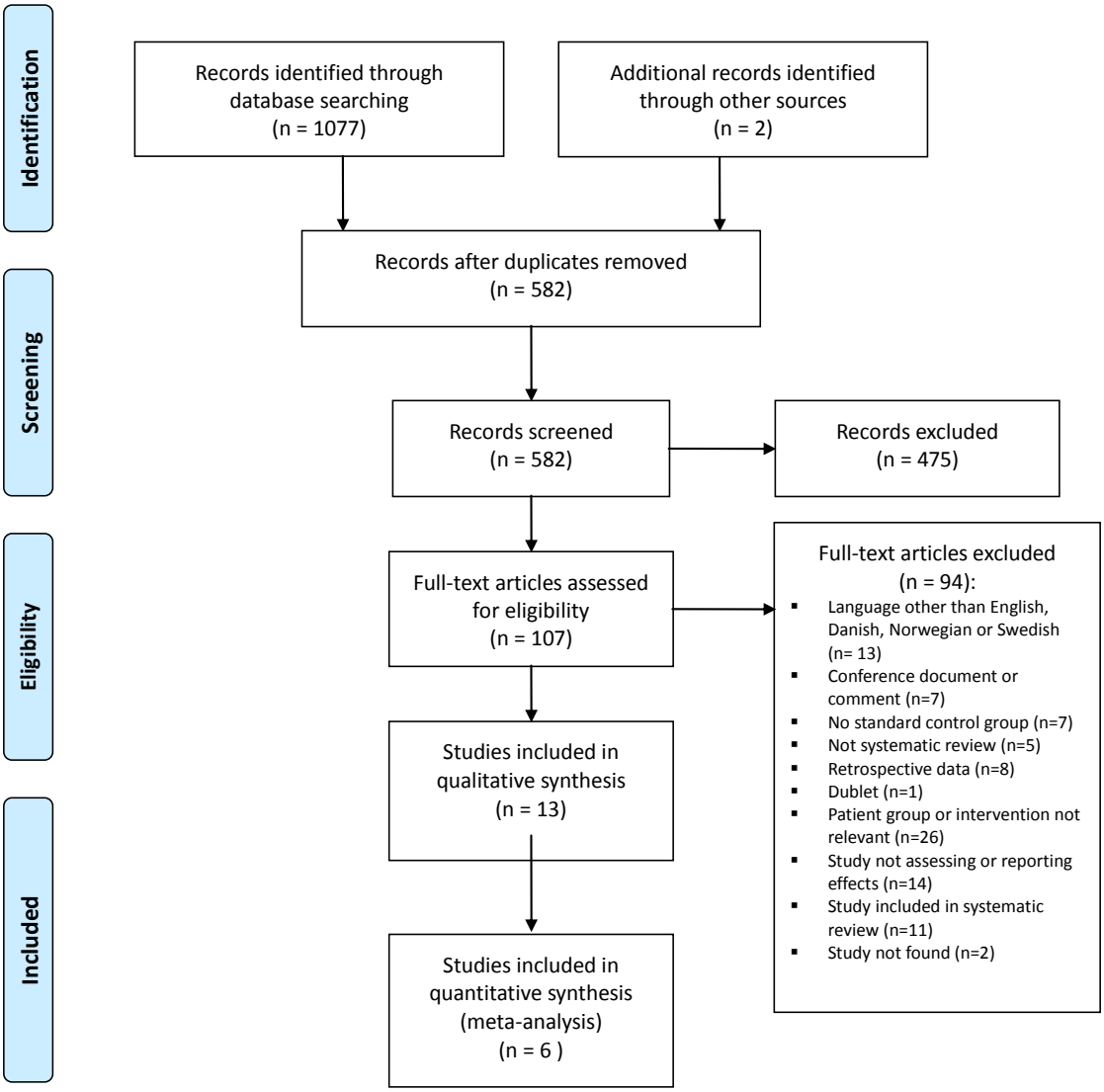
In addition to these systematic searches, clinical and technical experts were consulted to identify additional studies.

For the TEC, CUR, and SAF domains, information was identified through the systematic literature search, clinical and technical experts, manufacturers' submission files, and through internet searches on the topic.

After removal of duplicates, literature selection was performed independently by two researchers from DEFACTUM using the inclusion/exclusion criteria and according to the research question and PICO scheme. Disagreements were resolved by consensus. The PRISMA flow diagram (Figure 3.1) display the phases of literature selection.

3.4 Study selection

Figure 3.1: Flow chart of systematic literature search[1]



The search generated 1079 records, which reduced to 582 after removal of duplicates. These studies were then screened by title and abstract to identify potentially relevant studies, resulting in 107 eligible studies. Literature selection by full text review was conducted for the EFF and SAF domains at the same time, resulting in included 13 studies. This process was checked by the co-authors (Osteba).

3.5 Data extraction and analyses

Data from the included studies were extracted using a standardised data extraction form (see Table A.1 and Table A.2). Data extraction was performed independently by two DEFACTUM researchers. The process was double-checked by the co-authors (Osteba).

[1] http://www.prisma-statement.org/

For each outcome, an evidence profile was generated using the GRADEpro software[2]. Results from high-quality studies were given the most emphasis in the synthesis. Results were presented as a narrative synthesis. For the EFF domain, statistical summary estimates of associations across studies were if possible derived using random effects meta-analysis, anticipating clinical heterogeneity and with modelling allowing for differences in associations from study to study. Heterogeneity across studies was statistically assessed using the Q-test and quantified by the inconsistency (I^2) index, where I^2 represents the percentage of total variation across studies attributable to heterogeneity rather than (statistical) chance. In cases with substantial heterogeneity across studies (I^2>50%), the robustness of the results was checked using a fixed effects model. A result was considered robust if the point estimate based on the fixed effects analysis was within the confidence interval of the random effects analysis. Meta-analyses were performed using Review Manager (RevMan, the Cochrane Collaboration). A two-sided p-value of <0.05 was considered to be statistically significant in all analyses.

3.6 Quality rating

Study and outcome validity and level of evidence were assessed according to EUnetHTA guidelines. In the EFF and SAF domains, the review was prepared in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement[3]. The quality of the included reviews was assessed using the Risk of Bias in Systematic Reviews (ROBIS) tool[4]. This tool assesses four domains to cover key review processes: study eligibility criteria; study identification and selection; data collection and study appraisal; and synthesis and findings. The Cochrane risk-of-bias tool was used to assess the quality of the included RCTs according to the EUnetHTA Guidelines on medical devices for study and outcome level. Risk of bias in cohort and case-control studies was assessed using Scottish Intercollegiate Guidelines Network (SIGN)[5] methodology checklists. The quality of the body of evidence was assessed using Grading of Recommendations, Assessment, Development and Evaluation (GRADE). The quality assessment was performed independently by two DEFACTUM researchers. The process was double-checked by the co-authors (Osteba). Any disagreement was resolved by consensus. For the TEC and CUR domains, no quality assessments were applied, but multiple sources were used to validate potentially biased sources. Descriptive analyses of different information sources were applied.

3.7 Deviations from project plan

In relation to outcomes, function in knee patients was measured using the Knee Society Score (KSS) and Oxford Knee Scale. No results were found regarding the durability and longevity of the devices, and patient satisfaction was not specified as an outcome in any study and was not reported in any of the included RCTs or cohort studies.

[2] https://gradepro.org/

[3] http://www.prisma-statement.org/

[4] https://www.bristol.ac.uk/population-health-sciences/projects/robis/

[5] https://www.sign.ac.uk/checklists-and-notes.html

4 DESCRIPTION AND TECHNICAL CHARACTERISTICS OF TECHNOLOGY (TEC)

The research questions for this assessment refer to two types of technologies: implants and cutting guides for guiding surgical interventions. The intervention is 3D printed custom-made or customisable implants and cutting guides, and the comparator is standard produced implants and cutting guides. The difference between the intervention and the comparator is related to the way in which the guides and the implants are produced: by moulding in the case of standard care and by 3D printing in the case of the intervention. 3D printing is a process by which 3D objects are created layer-by-layer from raw materials guided by a digital file.

4.1 Research questions

Element ID	Research question
B0001	What are 3D printed implants and cutting guides versus standard implants and cutting guides?
B0002	What is the claimed benefit of 3D printed implants and cutting guides compared to standard implants and cutting guides?
B0003	What is the phase of development and implementation of 3D printed implants and cutting guides?
B0004	Who administers 3D printed implants and cutting guides and standard implants and cutting guides and in what context and level of care are they provided?
B0008	What kind of special premises are needed to use 3D printed implants and cutting guides and standard implants and cutting guides?
B0009	What equipment and supplies are needed to use 3D printed implants and cutting guides and standard implants and cutting guides?
A0020	For which indications have 3D printed implants and cutting guides received marketing authorisation (FDA or CE marking)?

Definitions

Custom-made manufacturer - The natural or legal person who undertakes the design of the product and manufactures the device to a predefined specification (i.e., a prescription).

Custom-made medical device - Any device specifically made in accordance with a duly qualified medical practitioner's prescription which gives, under their responsibility, specific design characteristics and is intended for the sole use of a particular patient.

Customisable medical device - Medical devices that are standard and are customised or adapted to the characteristics of a particular patient.

Cutting guide/surgical guide - A surgical guide is a small customised tool made from a sterilisable material that can be used short-term in a patient and that guides the saw and/or drill in the planned direction (https://www.xilloc.com/products_services/surgical-guides).

4.2 Results

3D printed and standard implants and cutting guides for knee, maxillofacial, and cranial replacements do not differ very much with respect to materials and final product characteristics. The main difference is related to the production process and the possibilities for customisation offered by 3D printing.

Features of the technology and comparators

[B0001] – What are 3D printed implants and cutting guides versus standard implants and cutting guides?

Figure 4.1 shows the production flow and the seven basic steps required when using 3D printed guides or implants for tissue replacement (3). The only difference in the process compared to the standard procedure for developing the mould is in steps 2 and 4. In steps 2 and 4, software design and printing are used instead of the usual standard device moulds. The number of steps and difficulties in printing a 3D device are dependent on device complexity. A general sequence is described below and in Figure 4.1:

Step 1. Device Design: This step consists of creating the most accurate model of the surfaces to be replicated and the volumes they refer to. In the case of 3D printing, this is achieved using imaging modalities such as computerised tomography (CT), ultrasonography, and/or magnetic resonance imaging (MRI). In the case of standard guides and implants, this is achieved using wax and soap models.

Step 2. Software Design: The second step consists of software design for 3D printing or moulding production in the case of standard implants and cutting guides.

Step 3. Material Control: All manufacturing processes require high-quality materials that meet consistent specifications to build consistent, high-quality devices. This step is identical in both types of production of implants and guides.

Step 4. Printing: When printing the implants or guides, different printers and materials are used depending on the material and the intended location. Different techniques are used as described below. In the case of standard devices, the mould is used to generate the implant guide using melted materials placed in the mould and hardened by different techniques, for example, freezing or using hardeners for some chemical substances.

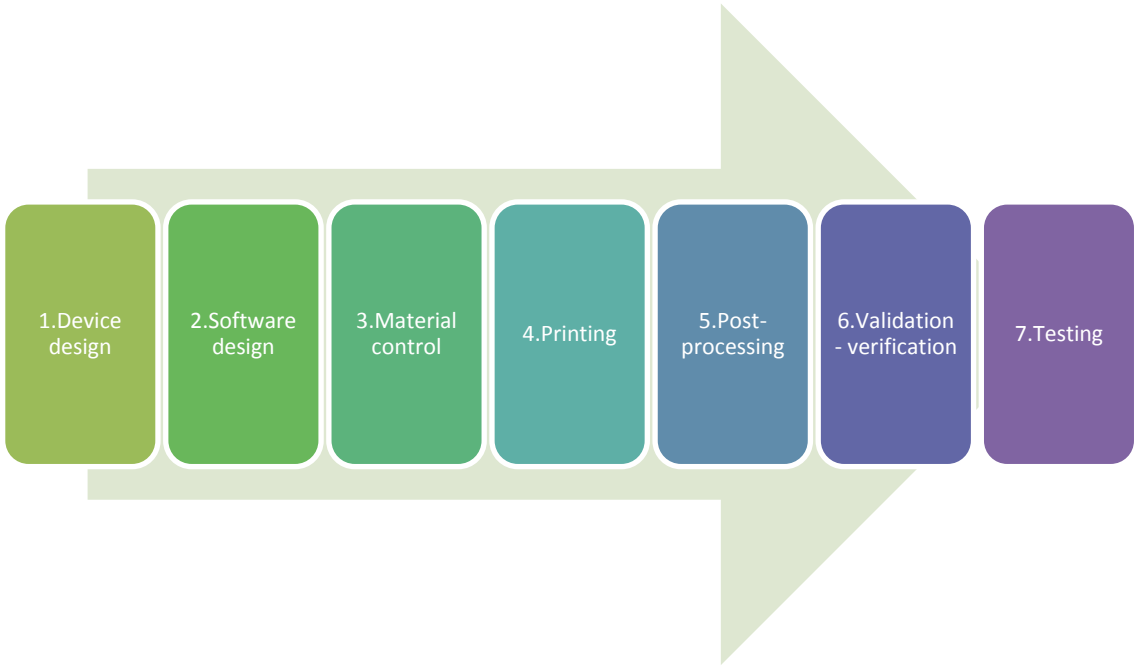
Step 5. Post-Processing: This step can also be the same in both standard and 3D printed devices. The design is tested and improved in terms of imperfections before being sterilised.

Step 6. Validation and Verification: This step is also the same in both processes, and it requires tests of usability and adequacy for the purpose for which it was designed.

Step 7. Testing: The two processes are again the same in this step. The processes in this step relate to the possible different requirements by regulation and the regulatory bodies in charge of certifying product safety and efficacy/performance (4,5)[6].

[6] 3D Print Exchange. National Institutes of Health; Available at: http://3dprint.nih.gov. Accessed July 12, 2018.

Figure 4.1: Process of 3D guide or prosthesis production. Modified from KCE, 2018 (3)



Although the materials used (6-10) and the 3D printing techniques are diverse, and a number of them can be used for the indications in this assessment, we only describe those that have been found and analysed in the included studies. Detail about the products and materials used in the studies is low, so it has been difficult to define the type of printer and material (powder, resin, droplet, or extrusion) used in production. Each material requires a different type of 3D printer and defines the final product characteristics and performance. Powder materials are 3D printed by selective laser sintering (SLS), resins by stereolithography (SLA), extrusion materials by fused deposition modelling (FDM), and droplets by multi-jet modelling (MJM). For more details see Appendix 3. The materials used for implants and cutting guides in 3D printing are the same as those that are normally used for cutting guides and implants when produced by standards methods. Table 4.1 details the materials and indications for commonly used materials in clinical use.

Table 4.1: Commonly used biomaterials in clinical use. Modified from Williams (11)

Material		Use
Metals	Titanium alloys	Dental implants, femoral stems, pacemaker containers, heart valves, fracture plates, spinal cages
	Cobalt–chromium alloys	Bearing surfaces, heart valves, stents, pacemaker leads
	Platinum group alloys	Electrodes
	Nitinol (nickel and Titanium alloy)	Shape memory applications
	Stainless steel	Stents, orthopaedic implants
	Magnesium and iron	Biodegradable metals for implants
Bioceramics	Alumina	Bearing surfaces
	Calcium phosphates	Bioactive surfaces, bone substitutes
	Carbon	Heart valves
	Zirconia	Bearing surfaces
Polymers	Ultra-high molecular weight polyethylene	Bearing surfaces
	PEEK	Spinal cages, cranial
	PMMA	Bone cement, intraocular lenses
	Polyurethane	Pacemaker lead insulation
	Expanded PTFE	Vascular grafts, heart valves
	Polyester textile	Vascular grafts, heart valves
Hydrogel	Silicones	Soft tissue augmentation, insulating leads, ophthalmological devices

Abbreviations: PEEK=polyether ether ketone; PMMA=poly(methyl methacrylate); PTFE=polytetrafluoroethylene

The materials and comparators included in this assessment are listed in Table 4.2.

Table 4.2: Type of materials and comparators* included in this report (based on the evidence from the included articles)

Product	Indication	Reference	Material	Type of printer	Comparator	
Guides	Maxillofacial	Mazzoni 2013	Cobalt-chrome-molybdenum		Standard reconstruction with indirect CAD / computer aided manufacturing procedure	
		Brandao 2016	Acrylic resin		Standard surgery	Without guides
		Ayoub 2014	PolyMide	Laser sintering	Standard surgery	Without guides
		Al-Ahmad 2013	Acrylic resin	Zcorp	Standard SSRO	Without guides
	Cranial					
	Knee	Huijbregts 2016			Standard instrumentation	Legion systems or Genesis II
		Boonen 2016			Standard instruments	
		Pfitzer 2014			Standard instruments	Journey
		Gan 2015	Acrylate resin	Stereolithography	Standard instruments	Scorpio posterior stabilised system
		Qiu 2017			Standard instruments	
		Zhang 2016		SPSS 350B solid laser prototyping	Standard instruments	Triathlon
		Thienpont 2017			Standard instruments	
		Mannan 2016			Standard instruments	
Implants	Cranial	Chrzan 2012	Polypropylene-polyester or aluminium-silicon	Milling Arrow 500	Standard instrumentation	Manually adjusted prosthesis
	Knee					
	Maxillofacial					

* No further data were obtained from the articles on comparators
Abbreviations: CAD=computer-aided design; SSRO=sagittal split ramus osteotomy

Regarding the manufacturers producing 3D printed implants and cutting guides in patients undergoing knee, maxillofacial, or cranial surgery, efforts were made to identify all relevant manufacturers and their products. However, it is a diverse market, so the list may not be exhaustive. Only a few manufacturers responded to direct inquiries made by the assessment team to help identify relevant products.

Table 4.3: Custom-made implants and custom-made surgical guides for cranio-maxillofacial surgery and orthopaedic traumatology surgery

Manufacturer	Relevant products	Webpage
Anatomics	AnatomicsC3D: Custom implants(cranial)	http://www.anatomics.com/
Arcam	EBM® for Orthopaedic Implants	http://www.arcam.com/solutions/orthopedic-implants/
Autodesk Within Medical	Novax DMA CEIT-KE	https://www.autodesk.com/products/within-medical/overview
Avinent	Personalised CAD/CAM implants and prostheses	https://www.avinent.com/eng/default.cfm
Bespokemedical	Bespoke solutions: 3D custom-made prostheses	https://bespokemedical.com.au/
Zimmer Biomet	The Signature™ System	https://www.zimmerbiomet.com.es/
CADskills BVBA	CADCAMise: Anatomical models, cutting/drilling guides and 3D print implants	https://www.cadskills.be/en
Cerhum SA	Medical ceramic 3D printing	https://www.cerhum.com/
CUSMED	No information found	No information found
EOS (3D printer producer)	3D printers for other manufacturers (e.g., Autodesk Within Medical)	https://www.eos.info/en
evonos GmbH & Co.	Evo-Shape: Skull implants	http://www.evonos.de/
Finceramica	CustomBone: Custom-made implant for cranioplasty	http://www.finceramica.it/
FIT Production	FIT production: Custom-made implants	http://www.fit-production.de/
Gsell	Gsell Medical: Implants	http://www.gsell.ch/en/home.html
implantcast GmbH	C-Fit 3D®: Patient-specific instruments and implants	https://www.implantcast.de/
Johnson & Johnson Medical (DePuySynthes)	TruMatch® cutting guides, for use with standard TKA (i.e., non-customised) implants (Sigma & Attune)	https://www.depuysynthes.com/ Johnson & Johnson have contributed with input to the project plan, 2nd draft assessment and by providing EUnetHTA submission files.
Kelyniam Global Inc.	Kelyniam Implants: Cranial implants	https://www.kelyniam.com/

Manufacturer	Relevant products	Webpage
KLS Martin Group	IPS Implants®: Implants and implant systems for cranio-maxillofacial surgery	https://www.klsmartin.com/de/
LayerWise NV	Metal additive manufacturing on demand	https://lrd.kuleuven.be/en/spinoff/cases/layerwise
Materialise	TruMatch CMF: Titanium 3D printed implant and patient-specific cranio-maxillofacial implants	https://www.materialise.com/en Materialise have contributed with input to the project plan, 2nd draft assessment and by providing submission files.
Mathys Orthopaedics	BalanSys and Affinis Architec	http://www.mathysmedical.com/en/homepage.html
Medacta International SA	MyKnee	https://www.medacta .com/
MedCAD	AccuModel®	https://medcad.net/
Mimedis AG	Mimedis®: Cutting guides and drill guides upon individual planning steps.	http://www.mimedis.com/
Optimus 3D	No customized products found	https://optimus3d.es/
OssDsign AB	OssDsign® Cranial: CAD technology and 3D printing	https://www.ossdsign.com/
OsteoSymbionics	ClearShield™: Craniofacial implants	http://pdf.medicalexpo.com/pdf/osteosymbionics/osteosymbionics-implants/90075-147775.html
Raomed SA	Custom-made implants and custom-made surgical guides for cranio-maxillofacial surgery and orthopaedic traumatology surgery	http://www.raomed.com.ar/home Has contributed with input to the 2nd draft assessment.
ResMed	Narval	https://www.resmed.com/epn/en/index.html
Smith & Nephew	Visionaire: PMI total knee system	https://www.smith-nephew.com/espana/
Stryker Corporation	Triathlon Knee System	https://www.stryker.com/
3DCERAM	3DCERAM custom-made or small series of bone substitutes skull implants	http://3dceram.com/
3D-Side	3D Model: Patient-specific anatomical model	https://www.3dside.eu/en
3D Systems	3D Systems Healthcare	https://es.3dsystems.com/
Synimed	Synicem ISM: Cranioplasty custom-made implants.	http://www.synimed.com/
Tecres	Cranos	https://www.tecres.it/en/home
Tissue Regeneration Systems inc.	TRS (Tissue Regeneration Systems) technology	https://www.tissuesys.com/
Xilloc	Patient-specific implants and surgical guides	https://www.xilloc.com/
4webmedical	Osteotomy Truss System™	https://4webmedical.com/

Abbreviations: CAD=computer-aided design; CAM=computer-aided manufacturing; PMI=patient-modelled instrument; TKA=total knee arthroplasty

Some manufactures have been identified in the later stage of the project, based on the suggestion of external experts. Therefore they were not consulted on the project plan.

After identifying the manufacturers and their products, two main issues needed clarifying: 1) which manufacturers made 3D printers for different purposes and with applications for medical purposes; and 2) which manufacturers used those 3D printers for medical purposes, especially those relevant to the scope of this report (6,7). Although this difference might be considered irrelevant, it is, however, relevant from the safety and legal points of view, i.e., whether the manufacturer is simply selling 3D printers for different purposes which *can* be used for medical purposes or if they are also involved in the design and production of medical devices. In fact, some manufacturers do either or both.

Table 4.4 shows the manufacturers, their products, and their characteristics. Most manufacturers did not directly provide information despite several attempts to make contact. Therefore, the analysis presented in Table 4.4 is based on publicly available information obtained from manufacturers' webpages, brochures, and elsewhere. The information is not to be considered exhaustive and might contain inaccuracies.

Table 4.4: Custom-made or customisable 3D printed implants and cutting guides in patients undergoing knee, maxillofacial, or cranial surgery. Shown are the manufacturers, products, locations, type of products and materials used

	Relevant products	Anatomical location	Guide	Prosthesis	Material 1	Material 2	Material 3
	3D Ceram	Cranial		X	Ceramics		
		Maxillofacial		X	Ceramics		
3D-Side	SkullPT	Cranial		X	Bone cement		
	Adaptive SkullPT	Cranial			Bone cement		
Anatomics	Durashield	Cranial		X	Silicone		
	Biomodel Stereotaxy	Cranial	X				
		Cranial		X	Acrylic (polymethyl metha-crylate)	Porestar (porous poly-ethylene)	Titanium
		Facial		X		Porestar (porous poly-ethylene)	Titanium
	Biomodels		X				
	Mandible templates & guides	Facial	X	X			
	Cranial templates	Cranial	X	X			
Bespokemedical		Knee		X			
Zimmer Biomet	Persona®; Vanguard; NexGen	Knee		X	Bearing materials: Vivacit-E vitamin E highly crosslinked polyethylene; E1® antioxidant-infused polyethylene; Pro-long® highly crosslinked polyethylene; Durasul® highly crosslinked polyethylene	OsseoTi® Porous Metal Technology	
	Encompass IM, Midface	Maxillofacial	X	X	PEEK	Polymer	Titanium
	HTR PEEK, HTR PMMA, Cranio-curve®, ThinFlap™, SterileTrac™, RapidFire®	Cranial	X	X	Idem	Idem	Idem
CADskills BVBA		Cranial	X	X	Titanium, PEEK	CADskills has developed a new UHMWPE specifi-cally treated to increase wear resistance. The method is undisclosed. The UHMWPE is en-riched with vitamin E, a potent antioxidant. These characteristics make this	Cutting guides are 3D printed in a class 1 bio-compatible resin that is autoclava-ble. The material is specially devel-oped for printing precise surgical

	Relevant products	Anatomical location	Guide	Prosthesis	Material 1	Material 2	Material 3
						material especially suited for articulating surfaces	guides and similar devices
		Maxillofacial	X	X	Idem	Idem	Idem
Cerhum SA (for confidentiality reasons, final product not disclose)		Maxillofacial		X	Alumina	Zirconia	
		Cranial		X			
		Knee		X			
Evonos		Cranial		X	Titanium		
Finceramica	Customized Bone (USA only) / CustomBone	Cranial		X	Biomimetic ceramic		
Fit-production (Does not specify the type of implants)		Cranial		X	Titanium (EBM technology)		
		Maxillofacial		X			
		Knee		X			
Gsell		Knee		X	UHMWPE (Ultra high molecular weight polyethylene), PEEK, PEKK, CF, pyrolytic graphite		
Implantcast		Knee		X	Implavit: The majority of implants are made of a cobalt chrome molybdenum (CoCrMo)	Implatan: The raw titanium (TiAl6V4) alloy material	UHMWPE
Johnson & Johnson Medical (DePuySynthes)	TruMatch® cutting guides, for use with standard TKA (i.e., non-customised) implants (Sigma & Attune)	Knee	X				
Kelyniam		Cranial, craniofacial		X	PEEK, lightweight Biomaterial		
KLS Martin		Cranial		X	Titanium	Resorbable materials	
		Maxillofacial		X			
Materialise (Johnson & Johnson)	TruMatch®	Craniomaxillofacial	X	X	Titanium and polyamide (guides)		
	TruMatch®	Cranial	X	X	Titanium and polyamide (guides)		
		Knee	X		Polyamide		
Mathys Orthopaedics Ltd.	BalanSys	Knee		X			

	Relevant products	Anatomical location	Guide	Prosthesis	Material 1	Material 2	Material 3
Medacta International SA	GMK	Knee	X	X	Cobalt-chrome	UHMWPE	
MedCAD	AccuShape®	Cranial		X	PEEK		
		Craniofacial	X				
Mimedis (Medartis)		Craniofacial		X	Flexible		
OssDSIGN		Craniofacial		X	Titanium		
Osteosymbionics	ST-temporalis, PK-Shield	Craniofacial		X			
Raomed		Cranial	X	X	Titanium	PEEK	PMMA, polyamide
		Maxillofacial	X	X	Titanium	PEEK	Cr-Co-Mo, UHMWPE, PMMA, polyamide
Stryker Corporation		Cranial		X	MEDPOR and PEEK	Titanium	
		Maxillofacial	X	X	MEDPOR and PEEK	Titanium	
		Knee		X	Titanium		
Synimed	Synicem ISM	Craniofacial			Cements		
Tecres	Cranos	Cranial		X	Polymethylmethacrylate		
Tissue Regeneration Systems	TRS Scaffold Technology	Cranio-maxillofacial		X			
Xilloc		Cranio-maxillofacial		X	PEEK-OPTIMA®: polymeric biomaterial	TI6Al4V: Titanium alloy	PP/PES knitted yarn: polymeric knitted from yarn
4WEB Medical		Craniofacial	X		Polyamide	Metallic	

Abbreviations: *EBM=electron beam melting; PEEK=polyether ether ketone; PES=polyester; PMMA=poly(methyl methacrylate); PP=polypropylene; TKA=total knee arthroplasty; UHMWPE=ultra-high molecular weight polyethylene; X=available information about guide or prosthesis; Empty space=no information.*

[B0002] – What is the claimed benefit of 3D printed implants and cutting guides compared to standard implants and cutting guides?

The claimed benefit of the technology in relation to the comparator(s) is the personalisation and the customisation of cutting guides and implants and the possibility of "in-house" producing 3D printed solutions (12,13,14). Based on this personalisation and customisation, the manufacturers claim that safety, performance, and efficacy are improved compared with standard practice including the use of customisable implants. Some manufacturers have also claimed that in the case of certain guides and implants, especially maxillofacial and cranial implants in which standardisation is more complicated or costly, 3D printers could be a viable economic solution for single implants or cutting guides.

[B0003] – What is the phase of development and implementation of 3D printed implants and cutting guides?

3D printing technology is not yet fully or widely implemented, and the comparator is standard practice. Some commercialised solutions such as TruMatch® from Johnson & Johnson and TruMatch® CMF from Materialise have received US Food and Drug Administration (FDA) clearance through the 510(k) procedure (see Table 4.3). However, in most cases, 3D printing technology has been introduced as a research or innovative technology without clear moderate or high-level clinical evidence on its effects, and should therefore be considered under research premises. The comparator in the included studies is not always well described, making it difficult to describe the standard solutions in detail.

[B0004] – Who administers 3D printed implants and cutting guides and standard implants and cutting guides and in what context and level of care are they provided?

In general, the comparators and 3D printing technology are administered at the tertiary level of provision. This is not due to production requirements, rather the necessary implementation of the comparators in those premises or under this frame of provision (15). The use of standard implants and cutting guides requires skilled professionals and learning curves that guarantee quality implementation of the technology. Similarly, 3D printed implants and cutting guides are administered by certified professionals in accredited centres to ensure high quality provision of care, although the level of certification differs from country to country and in some countries any centre can provide the service and use the technology. The same level of expertise is required in those centres implementing or researching 3D printing solutions as those using standard implants or cutting guides. In cases where no regulatory approval of 3D printed solutions is needed, the use of 3D printed solutions is considered under research circumstances and thus details of the technology must be communicated to the patient and his/her caregiver as required as part of informed consent.

[B0008] – What kind of special premises are needed to use 3D printed implants and cutting guides and standard implants and cutting guides?

No special premises are required for the use of custom-made 3D printed devices compared to standard implants and cutting guides. The main differences are related to device production and not to their application and use in clinical practice.

[B0009] – What equipment and supplies are needed to use 3D printed implants and cutting guides and standard implants and cutting guides?

The equipment needed for using 3D printed devices is dependent on the organisation of the entire production process and how much of this production is in-house. The main equipment required for the 3D printing process is imaging processing systems and 3D printers. If the organisation is simply contracting production from external manufacturer, the equipment needed is similar to the equipment required to use standard implants and cutting guides.

[A0020] – For which indications have 3D printed implants and cutting guides received marketing authorisation (FDA or CE marking)?

Here it is necessary to differentiate between 3D printing market authorisation and CE marking of the final products/devices. 3D printers in themselves are not normally considered a medical device and receive CE marks as other technologies on the market. In the case of implants and cutting guides, it is unclear what authorisation is required, since the implants and cutting guides could be classified as custom-made or customisable. As all the devices in this assessment could be considered custom-made, the issue is that even as class III devices they do not need to bear the CE mark because they are custom-made. This does not, however, mean that they are not subject to regulatory control through post-market surveillance via competent authorities of the member states, where manufacturers are required to report incidents and maintain post-market surveillance.

However, some manufacturers, for example Johnson & Johnson and Materialise, have received CE or FDA authorisation, but the performance at the individual implant/cutting guide level still needs to be evaluated to establish the technology's value. So, the consideration of custom-made or customisable must be taken into account and their differentiation, when 3D printed, is not well defined. Until there is conclusive evidence of safety and efficacy, patients should be informed of the alternatives and the uncertainties of their use, with data being collected. Procedures such as those proposed by EUnetHTA JA3, WP5 for data collection post introduction should be followed to ensure data quality in those registries.

5 HEALTH PROBLEM AND CURRENT USE OF THE TECHNOLOGY (CUR)

5.1 Research questions

Element ID	Research question
A0002	Which diseases or health conditions most frequently lead to knee, maxillofacial, or cranial surgery?
A0004	What is the natural course of the disease or health condition?
A0005	What are the symptoms and the burden of disease or health condition for the patient?
A0006	What are the consequences of the disease or health condition for society?
A0024	How is the disease or health condition currently diagnosed according to published guidelines and in practice?
A0025	How is the disease or health condition currently managed according to published guidelines and in practice?
A0007	What is the target population in this assessment?
A0023	How many people belong to the target population?
A0011	How much are the technologies utilised?

5.2 Results

3D printed medical devices are used in a wide variety of indications. This assessment focuses on the following clinical areas in which 3D printed custom-made or customisable implants and cutting guides are most frequently applied and where most of the published evidence lies: knee, maxillofacial, and cranial surgery. The most frequent diseases in these clinical areas include knee osteoarthritis treated with total knee arthroplasty, oral cancer treated with mandibular reconstruction, and traumatic brain injury with intracranial hypertension treated with decompressive craniectomy (DC) and later cranioplasty (3, 16).

Overview of the diseases or health conditions

[A0002] – Which diseases or health conditions most frequently lead to knee, maxillofacial, or cranial surgery?

Knee osteoarthritis

The primary indication for total knee arthroplasty (TKA) is the relief of significant and disabling pain and improvement of functional status in patients with end-stage knee osteoarthritis (OA) (17). Two types of knee OA are recognised: primary knee OA is caused by progressive joint cartilage destruction over time without any apparent underlying cause, while secondary OA can be caused by trauma or surgery to the joint structures, congenital limb malformations, malposition (varus/valgus), or abnormal articular cartilage such as that found in end-stage rheumatoid arthritis (RA) (18).

Oral cancer

Invasive oral cancer is the primary indication for mandibular reconstruction, but it is also used for other diseases such as osteomyelitis and bisphosphonate-related osteonecrosis (19). Oral cancer includes a group of neoplasms affecting any region of the oral cavity, pharyngeal regions, and salivary glands. Oral squamous cell carcinoma (OSCC) is the most frequent (90%) oral neoplasm.

Traumatic brain injury

Cranial surgery with cranioplasty after decompressive craniectomy (DC) is widely used to treat intracranial hypertension (ICH) following traumatic brain injury (TBI), stroke, and other conditions associated with raised intracranial pressure (20).

[A0004] – What is the natural course of the disease or health condition?

Knee osteoarthritis

Knee OA is characterised by progressive destruction of the cartilage that lines the knee joints, the subchondral bone surfaces, and synovium. It is accompanied by pain, immobility, muscle weakness, and reduced function and activities of daily living (21). Knee OA is chronic and progressive and worsens over time with pain as the primary symptom. It starts with intermittent weight-bearing pain and develops to more persistent pain, especially if contributing factors (obesity, misalignment, and occupation) are not properly modified. Without treatment, OA eventually leads to significant pain and disability requiring surgical intervention (22). Knee RA is a chronic inflammatory disease characterised by synovial hyperplasia, bone loss, and joint deformity, which eventually leads to pain and disability requiring surgical intervention (23).

Oral cancer

Oral squamous cell carcinoma (OSCC) often presents as an ulcer with fissuring or raised margins or may present as a lump, a red, white or mixed white-red lesion, a non-healing wound, or with cervical lymph node enlargement (23). Despite advances in therapeutic approaches, OSCC prognosis is poor due to frequent aggressive local invasion, metastasis, and recurrence. The five-year survival rate ranges from 20-90% depending on which part of the oral cavity is involved and the stage. Patients diagnosed early have a better long-term survival (60-90%), whereas when diagnosis is late the long-term survival ranges from 20-50% (24).

Traumatic brain injury

TBI describes an injury to the head arising from blunt or penetrating trauma or acceleration/deceleration forces. It is associated with one or more of the following features: decreased level of consciousness, amnesia, objective neurological abnormalities, and skull fractures (25). The Glasgow Coma Scale (GCS) is used to triage patients early after TBI as an indicator of severity, with TBI graded as mild, moderate, or severe (25). After primary brain injury, there is a risk of secondary injury from intracranial hypertension (ICH) as a consequence of brain swelling or haemorrhage. ICH is the most frequent cause of death and disability following severe TBI (25) and is often treated with DC and later cranioplasty.

Effects of the disease or health condition

[A0005] – What are the symptoms and the burden of disease or health condition for the patient?

Knee osteoarthritis

For the individual, the burden of knee OA includes pain, limited activity, and markedly reduced quality of life. The intensity of clinical symptoms and rate of progression vary greatly from person to person. However, symptoms typically become more frequent and severe and cause progressive limitations in function over time, eventually leading to disability. Patients experience knee

pain that is gradual in onset and that worsens with activity, swelling and knee stiffness, and pain after prolonged sitting or resting (18). In a population in New Zealanders aged 40-84 years, knee OA accounted for 3.44 quality-adjusted life years (QALYs) lost per person, corresponding to 467,240 QALYs across the population. These QALY losses were higher for females than males due to a greater prevalence of knee OA and higher life expectancy (26).

Oral cancer

The initial stages are often painless. In later and larger lesions, symptoms vary from mild discomfort to severe pain. Other symptoms include ear pain, bleeding, mobile teeth, breathing problems, speech difficulties, dysphagia, problems using prostheses, trismus, and paraesthesia (27). Many oral cancer patients suffer from anxiety and depression which negatively impact their quality of life, and the suicide incidence is high in this patient group (28).

Traumatic brain injury

After TBI of any severity, many patients display cognitive and emotional difficulties and require assistance in their activities of daily living (25,29). Reduced health-related quality of life (HRQoL) has been identified in individuals with TBI compared with a healthy population (30).

[A0006] – What are the consequences of the disease or health condition for society?

Knee osteoarthritis

The knee is the most frequently affected joint in OA, and the societal and economic burden of this disease at a population level is substantial. Most of the direct costs are usually attributed to the healthcare system including hospital stays, orthopaedic surgery, medications, doctor visits, and other health professional visits. Indirect costs are also incurred that are attributable to productivity losses from absenteeism, presenteeism, early retirement, and premature death (31).

Oral cancer

Oral cancer is a significant public health concern. According to global estimates, oral cancer causes approximately 130,000 deaths per year (32). There is a heavy financial burden to society in treating oral cancer that includes direct costs for diagnosis, treatment, and hospitalisation and indirect costs including loss of productivity due to morbidity and disability (33).

Traumatic brain injury

TBI is a major public health problem worldwide and is the most common cause of death and disability in children and young adults. Over 50% of patients with severe TBI are moderate to severely disabled after one year, and many never recover to full independence (33). The costs for treating severe TBI result in a heavy financial burden to society, where the indirect costs of disability, lost wages, and lost productivity outweigh the direct medical costs including hospitalisation and rehabilitation (34).

Current clinical management of the disease or health condition

[A0024] – How is the disease or health condition currently diagnosed according to published guidelines and in practice?

Knee osteoarthritis

The diagnosis of knee OA can usually be made by clinical judgment and imaging performed by clinical experts, but these are not the only markers of knee OA. The European League Against Rheumatism (EULAR) has developed evidence-based recommendations for the diagnosis of knee OA (34). These include typical symptoms and signs, the use of imaging and laboratory tests, and differential diagnosis. Three symptoms (persistent knee pain, limited morning stiffness, and reduced function) and three signs (crepitus, restricted movement, and bony enlargement) were found to be most useful. The severity of knee OA can be staged using the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC), which reflects clinical symptoms divided into three subscales: pain, stiffness, and physical function (35).

Oral cancer

The diagnosis of OSCC is based on a thorough clinical examination of the oral mucosa and palpation of the lymphoid tissue of the neck to detect masses that represent metastases. The clinical findings should be verified with a biopsy to confirm the diagnosis histopathologically (27). The tumour-node-metastasis (TNM) classification is used to stage oral cancers (36).

Traumatic brain injury

There is no consensus on definitive diagnostic measures, but there is general agreement that a clear mechanism and suspicion of injury plus a minimum of one common clinical feature define a TBI. The diagnosis is based on injury history, clinical examination including GCS, and CT scans of the head (37).

[A0025] – How is the disease or health condition currently managed according to published guidelines and in practice?

Knee osteoarthritis

Knee OA is not currently curable, and the goal of non-operative treatment is to alleviate the signs and symptoms of the disease and to slow its progression. Conservative treatment is generally indicated in patients with generalised knee pain who wish to delay undergoing a surgical procedure. According to EULAR recommendations, conservative treatment of knee OA should proceed in a stepwise fashion including physical and physiotherapeutic measures, orthopaedic aids, weight loss, and drug therapy (34). Despite conservative treatment, many with severe knee OA require a TKA as the definitive treatment (35).

Oral cancer

The treatment of OSCC consists of surgery, radiotherapy, and chemotherapy. OSCC is typically treated by one or a combination of these modalities according to tumour location and stage (38).

Traumatic brain injury

DC is used as a therapeutic strategy for refractory cerebral oedema in cases when first-line non-invasive methods fail (29). Cranioplasty is then performed not only for aesthetic reasons but also to protect the underlying neural tissue and improve its perfusion and metabolism (39).

Target population

[A0007] – What is the target population of this assessment?

Knee osteoarthritis

The incidence and prevalence of knee OA have increased over recent decades at least in part due to an aging population and the rising prevalence of obesity (40). Knee OA affects at least 19% of adults aged 45 years, and >50% of patients over 65 years have radiographic changes in the knee indicating arthritis, although many patients are asymptomatic until after age 65 years (41,42). Moreover, the occurrence of knee OA in younger active people is reported to be increasing (40). The global prevalence of radiographically confirmed symptomatic knee OA in 2010 was estimated to be 3.8% (40).

Oral cancer

OSCC is most common in older males with a history of tobacco and alcohol consumption, in lower socio-economic groups, and in ethnic minority groups (36). However, some studies have shown a high frequency of OSCC in younger adults (aged <40 years), probably due to changes in lifestyle habits in this age group such as changes in tobacco and alcohol consumption as well as exposure to biological agents such as human papillomavirus (HPV) (43).

Traumatic brain injury

TBI is most common in children and young adults (25).

[A0023] – How many people belong to the target population?

Knee osteoarthritis

In Denmark, which has approximately 5.5 million inhabitants, 60,000 people each year with symptoms of knee arthritis seek medical advice[7]. In the USA, knee OA accounts for over 80% of all OA and affects at least 19% of adults aged 45 years and older (42). The number of people in the target population with symptomatic OA is likely to increase due to the aging population and the rise in the prevalence of obesity (44).

Oral cancer

Worldwide, oral cancer accounts for 2-4% of all cancer cases, corresponding to 300,000 new cases diagnosed in 2012 (45). Age-standardised oral cancer incidence rates vary between 0.9 per 100,000 women in Eastern Asia to 24.0 per 100,000 men in Melanesia.

[7] [www.sst.dk/da/udgivelser/2012/nkr-og-faglige-visitationslinjer-knaeartrose]

Traumatic brain injury

It is estimated that TBI affects over 10 million people annually worldwide, leading to either mortality or hospitalisation (46).

[A0011] – How much are the technologies utilised?

Knee osteoarthritis

The total number of primary and revision TKAs in Europe was estimated to be 1,324,000 each year in 2011, whereas the number of patient-specific instrument (PSI) procedures was 17,515, corresponding to 1.3% of total (1,2).

Oral cancer

The mandibular reconstruction with free fibula flap is currently regarded as the gold standard reconstruction of large segmental mandibular defects caused by benign or malignant disease (47). Mandibular reconstruction has changed significantly over the years and continues to evolve with the introduction of newer technologies and techniques. 3D printing is a rapidly growing technology in medicine, and when mandibular reconstruction is performed with a fibula free flap with 3D printed models, the long bone can be reconfigured into a 3D angular structure (48). There are no available published data on the utilisation of these technologies in Europe.

Traumatic brain injury

There are no available published data on the utilisation of either standard cranioplasty or with 3D printed materials.

6 CLINICAL EFFECTIVENESS (EFF)

6.1 Research questions

Element ID	Research question
D0001	What is the expected benefit of 3D printed implants and cutting guides on mortality?
D0005	How does use of 3D printed implants and cutting guides affect symptoms and findings (severity, frequency) of patients undergoing surgery?
D0006	How do 3D printed implants and cutting guides affect progression (or recurrence) of the disease or health condition?
D0011	What is the effect of 3D printed implants and cutting guides on patients' body functions?
D0016	How does the use of 3D printed implants and cutting guides affect activities of daily living?
D0012	What is the effect of 3D printed implants and cutting guides on generic health-related quality of life?
D0013	What is the effect of 3D printed implants and cutting guides on disease-specific quality of life?
D0017	Were patients satisfied with the use of 3D printed implants and cutting guides?

6.2 Results

Included studies

Thirteen studies reported clinical effectiveness outcomes (19,39,49-59). Eight studies (six RCTs (49-54) and two SRs (55,56) reported on patients undergoing knee reconstruction; four studies (three RCTs (19,58,59) and one prospective study (57) reported on maxillofacial patients (more specifically patients undergoing mandibular reconstruction); and one prospective study examined patients undergoing cranioplasty (39). Details of the studies are provided in Table A1 and Table A2. Studies published between 2012 and 2017 had follow-up periods of between one and 44 months.

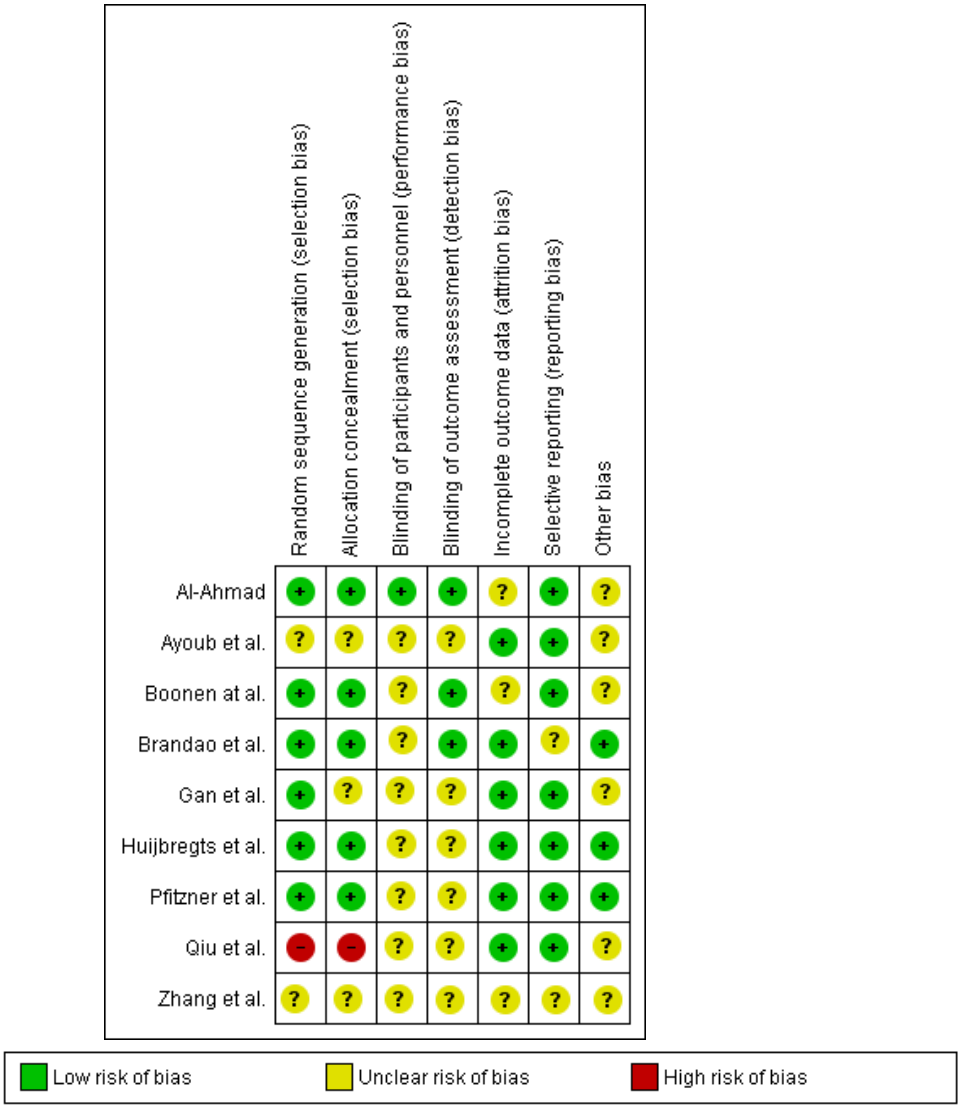
Results are presented according to the research questions categorised in relation to specific outcomes and finally patient group. Not all patient groups are represented under a specific outcome, since some outcomes relate to particular patient groups, e.g., the outcome 'number of outliers' only includes results from knee arthroplasty patients.

The quality of the two included cohort studies by Chrzan et al. (39) and Mazzoni et al. (57) was low. However, the quality of the two SRs by Thienpont et al. (55) and Mannan et al. (55,56) was high. Studies included in the two SRs were of moderate to high quality. The quality of the included RCTs was in general moderate, although one study by Qui et al. (53) was low quality. Blinding was the criterion most often described unevenly. Reporting of the blinding status of study participants, personnel, and assessors was in general incomplete, making the risk of bias unclear. Tables 6.1 and 6.2 present the risk of bias of the RCTs and SRs.

Table 6.1: ROBIS results on selected systematic reviews

Review	Phase 2				Phase 3
	▪ 1. STUDY ELIGIBILITY CRITERIA	▪ 2. IDENTIFICATION AND SELECTION OF STUDIES	▪ 3. DATA COL-LECTION AND STUDY APPRAIS-AL	4. SYNTHESIS AND FINDINGS	RISK OF BIAS IN THE REVIEW
Thienpont	▪ ☺	▪ ☺	▪ ☺	▪ ☺	▪ ☺
▪ Mannan	▪ ☺	▪ ☺	▪ ☺	▪ ☺	▪ ☺

Table 6.2: Cochrane risk of bias results on RCTs



Mortality

[D0001] What is the expected benefit of 3D printed implants and cutting guides on mortality?

Mortality was not specified as an outcome in any study and was not reported in any of the included RCTs or cohort studies.

Morbidity

[D0005] – How does use of 3D printed implants and cutting guides affect symptoms and findings (severity, frequency) of the patients undergoing surgery?

[D0006] – How do 3D printed implants and cutting guides affect progression (or recurrence) of the disease or health condition?

Number of outliers (by >3°) in TKA: 3D print vs. standard implants and cutting guides in patients undergoing knee reconstruction

Hip-knee-ankle angle (limb), alignment, or mechanical axis (Figure 6.1)

The number of outliers in TKA was reported in four RCTs (49,51-53) and one SR (55). Data from all four primary studies were included in the meta-analysis. The odds ratio calculated using the number of events in the two groups was 0.28 (95% CI 0.12-0.66; p=0.003) favouring 3D print technology (cutting guides; low quality of evidence). There was a low degree of heterogeneity between the studies (I^2=33%, p=0.21) (Figure 6.2).

The SR by Thienpont et al. (55) reported a pooled relative risk of 0.79 (95% CI 0.65-0.95; p=0.013) favouring PSI/3D print technology. Mechanical axis deviation (by >3°) was the primary endpoint in the SR, which included 44 RCTs and cohort studies.

Figure 6.1. Hip-knee-ankle angle, mechanical axis, coronal femoral angle, and coronal tibial angle. Source: Jan Hejle, anatomi.dk

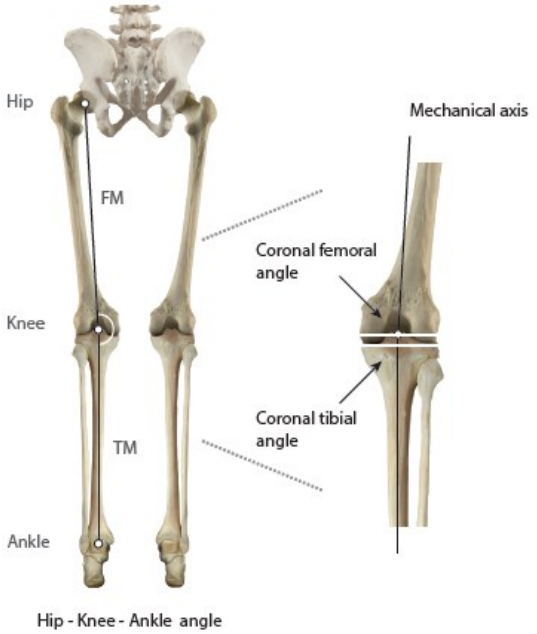
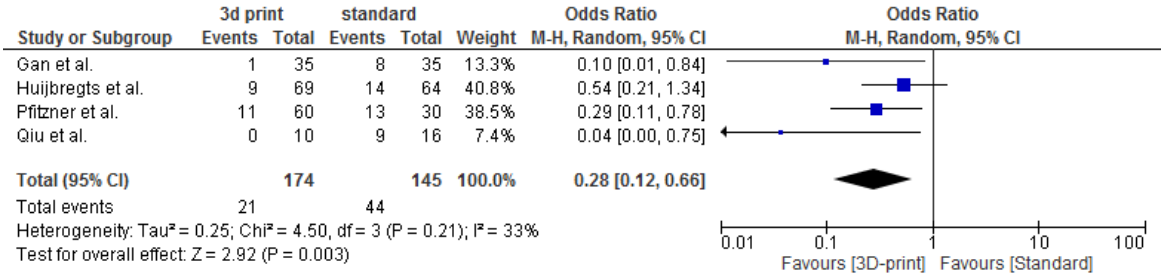


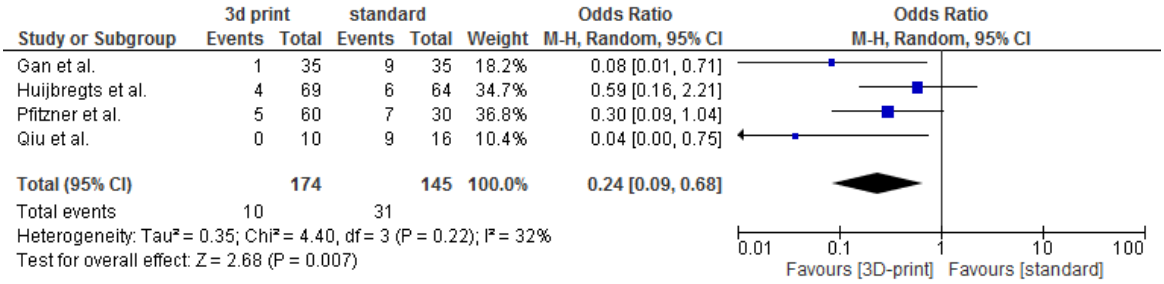
Figure 6.2: 3D print vs. standard; outcome: proportion of outliers (>3°), hip-knee-ankle angle



Coronal femoral angle

Coronal femoral angle, which describes implant alignment measured between the mechanical femoral axis and the tangent of the distal femoral condyles (51) (Figure 6.1), was assessed in four RCTs (49,51-53) and one SR (55). The odds ratio was statistically significant at 0.24 (95% CI 0.09-0.68; p=0.007) and favoured 3D print technology (low quality of evidence). There was a low degree of heterogeneity between studies (I^2=32%, p=0.22) (Figure 6.3). The SR by Thienpont et al. (55) reported a relative risk of 0.74 (95% CI 0.55-0.99; p=0.043) in favour of PSI/3D print technology.

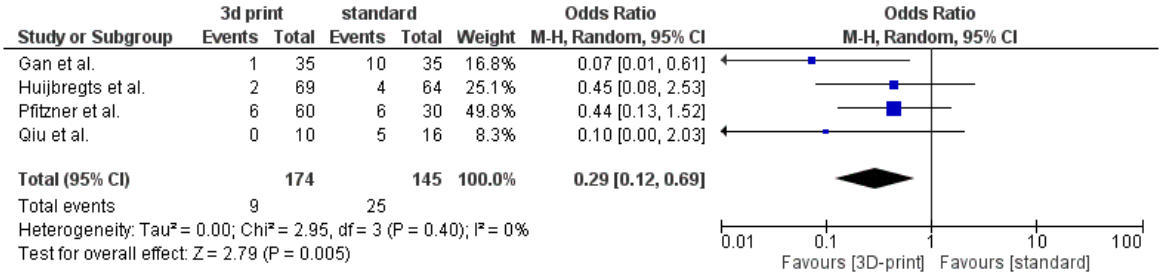
Figure 6.3: 3D print vs. standard; outcome: proportion of outliers (>3°), coronal femur



Coronal tibial angle

The coronal tibial angle, which describes the angle between the mechanical tibial axis and the tangent at the implant-bone interface of the tibia (51) (Figure 6.1), was assessed in four RCTs (49,51-53) and one SR (55). The odds ratio was statistically significant at 0.29 (95% CI 0.12-0.69; p=0.005) and favoured 3D print technology (low quality of evidence). There was no heterogeneity between studies (I^2=0%, p=0.40) (Figure 6.4). Thienpont et al. (55) reported an insignificant relative risk of 1.30 (95% CI 0.92-1.83; p=0.13).

Figure 6.4: 3D print vs. standard; outcome: proportion of outliers (>3°), coronal tibial angle



Tibial slope

The tibial slope or sagittal tibial alignment is defined as the angle between the anterior tibial cortex and the tangent of the implant's inferior surface (Figure 6.5) (51). It was assessed in three RCTs (49,51,53) and one SR (55). As with the coronal alignment outliers, the tibial slope outlier was defined as deviation of >3° from the planned alignment, which is normally intended to be a posterior slope of 3°. The analysis showed inconsistent results, and the odds ratio was not statistically significant at 0.55 (95% CI 0.07-4.43; p=0.57) (very low quality of evidence). Also, there was high heterogeneity between studies (I^2=86%, p<0.001) (Figure 6.6). However, the point estimate of 0.55 was found to be robust based on the fixed effects analysis, which showed a point estimate of 0.91, well within the confidence interval of the random effects analysis. The SR by Thienpont et al. (55) reported a relative risk of 1.32 (95% CI 1.12-1.56; p=0.001) in favour of standard surgery.

Figure 6.5: Tibial slope angle. Source: Jan Hejle, anatomi.dk

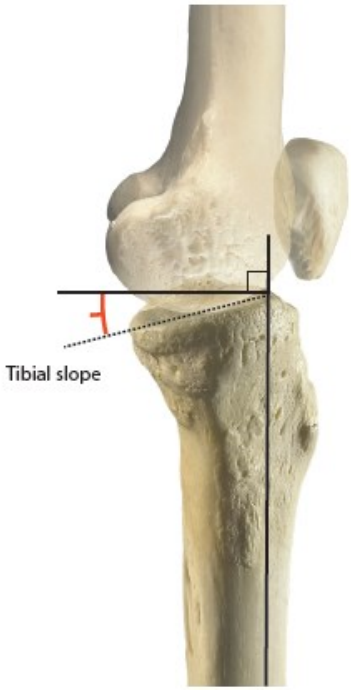
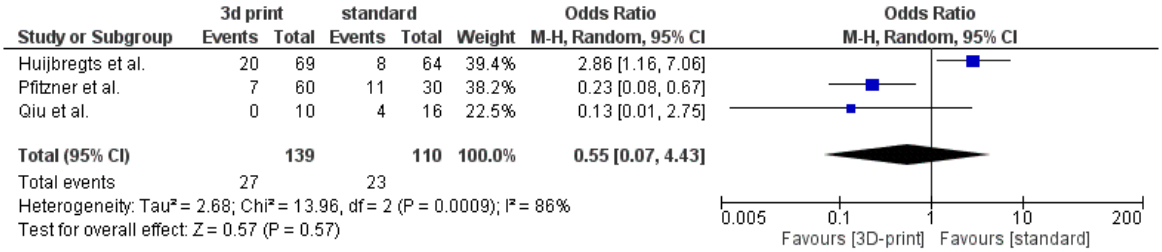


Figure 6.6: 3D print vs. standard; outcome: proportion of outliers (>3°), tibial slope



Femoral rotation

Rotation of the femoral component can be defined as the angle between the posterior condylar line and the epicondylar axis (Figure 6.7) (49). This was measured in two RCTs (49,51) and one SR (55). The analysis showed an insignificant odds ratio of 0.33 (95% CI 0.07-1.56; p=0.16; low quality of evidence) with a tendency favouring 3D printing. High heterogeneity was present between the studies (I^2=73%, p=0.05), but the result was robust (Figure 6.8). Thienpont et al. (55) also found no difference between groups, reporting a relative risk of 0.97 (95% CI 0.69-1.38; p=0.88).

Figure 6.7: Femoral rotational angle. Source: Jan Hejle, anatomi.dk

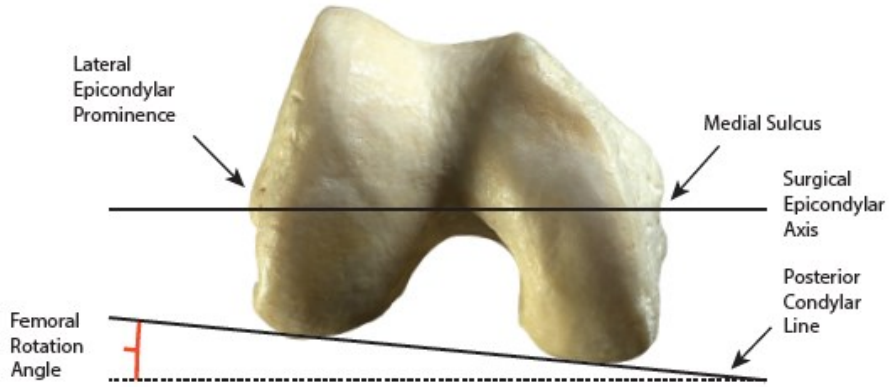
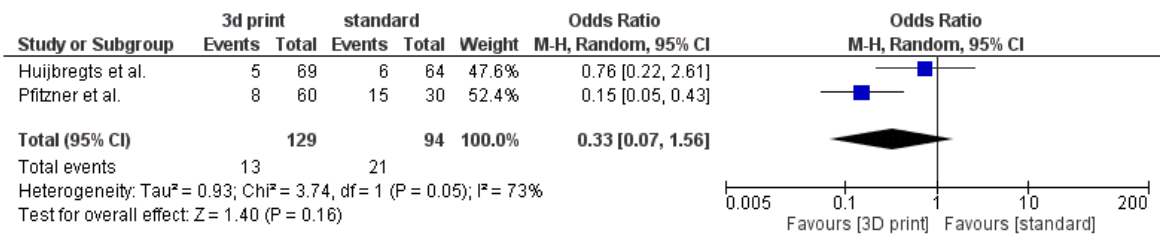


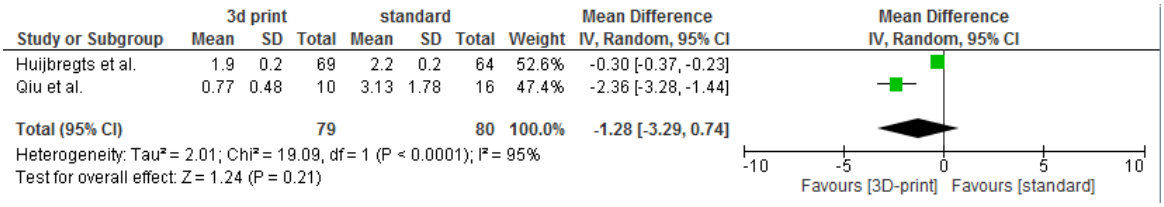
Figure 6.8: 3D print vs. standard; outcome: proportion of outliers (>3°), femoral rotation



Absolute deviation in degrees (hip-knee-ankle angle): 3D print vs. standard implants and cutting guides in patients undergoing knee reconstruction

Absolute deviation in degrees was reported in five studies (49,51-54). Two studies reported hip-knee-ankle angle as mean values (49,53). The meta-analysis showed a small and statistically insignificant pooled estimate of -1.28° (95% CI -3.29-0.74; p<0.0001) in support of 3D print technology (very low quality of evidence). There was a high degree of heterogeneity between studies (I^2=95%, p<0.0001), but the result was robust (Figure 6.9). Gan et al. (52) found a significant difference of 4° in the mechanical limb axis in support of the 3D print group (navigational template) compared to standard, but no standard deviation was reported (52). Pfitzner et al. (51) found a significant difference of 1.5° and 3.5° in the CT-based and MR-based patient-specific instrumentation groups (3D print), respectively, compared to standard surgery (51).

Figure 6.9: 3D print vs. standard; outcome: absolute deviation in degrees, hip-knee-ankle angle



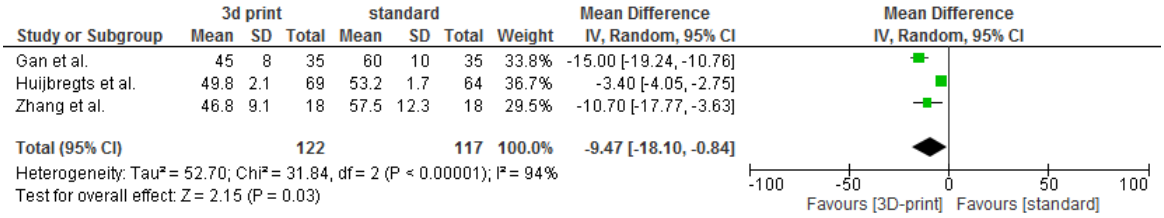
Regarding other alignment assessments, most studies reported absolute deviations in the coronal femoral component, coronal tibial component, and tibial slope component. The absolute deviation in the coronal femoral component in all five studies (51,53,54) was reported to be significantly and consistently smaller in the 3D print groups than in standard groups, although median/mean differences were minor (0.3°-2.0°) between groups. The absolute deviation in the coronal tibial component in four studies (51-54) was significantly smaller in the 3D print groups than in standard groups, with median/mean differences of 1.0°-2.0° between groups. Huijbrechts et al. (49) found no difference between the groups.

The posterior tibial slope component was reported in five studies (49,51-54). In three studies (49,52,53), the absolute deviation was found significantly higher in the 3D print groups than in the standard groups, with differences of 0.1°-1.7°. In two studies, deviation in the tibial slope component was significantly smaller (2.5°-4.1°) in favour of the 3D print groups (51,54).

Operating time: *3D print vs. standard implants and cutting guides in patients undergoing knee reconstruction*

Operating time was measured and reported in four RCTs (49,51,52,54) and one SR (55). Huijbrechts et al. (60) reported that reduced operating time may increase surgical efficiency and potentially reduce surgical complications. Pooled results from three studies showed a significant estimate of 9.47 minutes shorter operating time favouring 3D print technology (95% CI 0.84-18.1; p=0.03; low quality of evidence) (Figure 6.10). There was a high degree of heterogeneity between studies (I^2=94%, p<0.0001); however, the analysis found the result to be robust. In the study by Zhang et al. (54), operating time in the 3D print group was 10.7 minutes shorter than in the standard group (p<0.01). A minor significant difference of 4.4 minutes (95% CI 1.7-7.2) in favour of 3D print technology was also found in the SR by Thienpont et al. (55).

Figure 6.10: 3D print vs. standard; outcome: operating time, patients undergoing knee reconstruction



3D print vs. usual care in maxillofacial surgery patients

Operating time was assessed in one randomised study of four studies evaluating computer-assisted mandibular reconstruction (19). Operating time was the main outcome. The operating time was presented in terms of six outcomes: a) shaping time at the donor site, significant difference in favour of standard group, 37.8 min vs. 62.1 min; b) shaping time at the defect site, significant difference in favour of 3D print group, 6.2 min vs. 20.3 min; c) time for osteosynthesis, significant difference in favour of 3D print group, 10.1 min vs. 18.2 min; d) overall reconstruction time (which includes time to shape the transplant and perform the osteosynthesis), significant difference in favour of 3D print group, 16.4 min vs. 38.5 min ($p<0.001$); e) ischaemic time (time from dissection of the transplant until perfusion is restored), significant difference in favour of 3D print group, 96.1 min vs. 122.9 min ($p<0.005$); and f) overall operating time, no difference between the groups, 498.5 min vs. 525.2 min ($p=0.527$). Further, no difference was found in ICU time and postoperative hospitalisation time.

3D print vs. usual care in cranioplasty patients

Using 3D print imaging and print technology reduced the time of cranioplasty neurosurgery by 16.2 minutes ($p<0.001$) in a group of 19 patients compared to a control group of 20 patients (very low quality of evidence) (39).

Visual analogue scale (VAS)

One study reported pain one and two years postoperatively in patient undergoing TKA and found no difference between 3D print and standard groups ($p=0.227$) (50).

Blood Loss

Blood loss or blood transfusion was assessed in two RCTs (52,54) and one SR (55) on patients undergoing knee reconstruction and in one RCT of maxillofacial surgery patients (19). In two studies (19,54), there was no difference in blood loss between the groups, and in two other studies (52,55), there was a significant difference in blood loss in favour of the 3D print groups, with a mean difference of 38 and 90 ml, respectively. Although significant, these differences were of no clinically relevant value.

Precision

Precision or accuracy was evaluated in one small prospective study of low quality in patients undergoing mandibular reconstruction (57). The study results can only be indicative of the effect of 3D printing technology in this area. Mazzoni et al. (57) found no difference between groups in patients undergoing prosthetically guided mandibular reconstruction with respect to midline deviation (vertical and horizontal), mandible angle-shift right, angular deviation of the mandibular arch,

and condyle position left. Significant differences in favour of the 3D intervention were reported for the outcomes mandible angle-shift left (mean 1.4 mm vs. 5.042 mm; p<0.006) and condyle position right (mean 1.297 mm vs. 4.458 mm; p=0.035).

Changes in sensory function

Changes in sensory function were evaluated in only one small RCT of moderate quality in patients undergoing bilateral sagittal split ramus osteotomy (SSRO) in a split-mouth design (59). SSRO can sometimes result in postsurgical neurosensory disturbance. Al-Ahmad et al. (59) investigated whether or not a computer-assisted surgical guide for SSRO more effectively reduced the incidence and severity of neurosensory complications than standard SSRO. With respect to tactile threshold, 67% of patients in the computer-assisted SSRO group had an abnormal threshold after one week in the lower lip and chin vs. 83% in the standard SSRO group (p<0.05). The tactile threshold was also significantly different in the chin after three months and the lower lip after six months. Likewise, two-point discrimination was significantly different in favour of the computer-assisted SSRO group in the lower lip at one week and the chin at six months (p<0.05). Other outcome measures, including direction of brush stroke and intraoperative parameters assessed by the surgeon, were equivalent between groups.

[D0011] – What is the effect of 3D printed implants and cutting guides on patients' body functions?

[D0016] – How does the use of 3D printed implants and cutting guides affect activities of daily living?

Function and activities of daily living were examined using two knee assessment scores, an osteoarthritis index, and clinical examination (in Brandao et al. (58)). Three RCTs (49-51) and two SRs (55,56) examined patients undergoing knee reconstruction, and one RCT examined mandibular reconstruction patients.

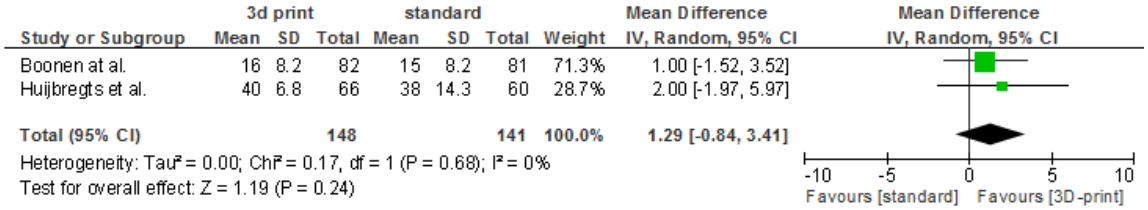
Knee Society Score (KSS)

The KSS was developed as a simple, objective way to measure a patient's function before and after TKA. KSSs range from 0 to 100, with 0 being the worst outcome and 100 being the best possible outcome. KSSs were reported in two RCTs and two SRs. In the two RCTs by Pfitzner et al. (51) and Boonen et al. (50), the scores were almost equivalent between groups in follow-up ranging from three months to two years, although pre- to post-operative scores increased radically (50,51). The two SRs by Thienpont et al. (55) and Mannan et al. (56) did not report any differences in knee scores, but Thienpont et al. (55) reported a mean difference in KSS in favour of the 3D print group of 4.3 points (95% CI 1.5-7.2; p=0.003). This difference is not considered to be of clinical significance (50).

Oxford Knee Scale

The Oxford Knee Scale was reported in three studies (49,50,56). The meta-analysis showed a small and statistically insignificant pooled mean difference of 1.29 (95% CI -0.84-3.41; p=0.24) points in support of 3D print technology (moderate quality of evidence). There was a low degree of heterogeneity between studies (I^2=0%, p=0.68; Figure 6.11). Mannan et al. (56) reported a statistically insignificant pooled mean difference of 0.48 points in support of standard surgery. Thus, the results can be regarded as imprecise and inconsistent using this scale (56).

Figure 6.11: 3D print vs. standard; outcome: Oxford Knee Score, patients undergoing knee reconstruction



Quality of life

[D0012] - What is the effect of 3D printed implants and cutting guides on generic health-related quality of life?

[D0013] - What is the effect of 3D printed implants and cutting guides on disease-specific quality of life?

Quality of life: SF12, EQ5D, and OHIP14 scores

Health-related quality of life (HRQoL) was evaluated in three RCTs (49,50,58): two in patients undergoing knee reconstruction (49,50) and one in mandibular reconstruction patients (58). Studies were of moderate quality. HRQoL was measured using the generic scores SF12 (Physical and Mental Component) and EQ5D, and the disease-specific OHIP-14 score (Oral Health Impact Profile) to evaluate the impact of interventions on oral HRQoL.

Huijbrechts et al. (49) reported that physical and mental SF12 scores were not significantly different at three months (p=0.418 and p=0.267, respectively) or at one year (p=0.114 and p=0.569) post-operatively. Likewise, Boonen et al. (50) reported equal progressions in the intervention and standard groups using the EQ5D score. OHIP-14 scores in mandibular reconstruction patients showed a significant difference in favour of the 3D printed group (p=0.027) (58).

Patient satisfaction

[D0017] - Were patients satisfied with the use of 3D printed implants and cutting guides?

Satisfaction was not reported in any study as an outcome and was not reported in any of the included RCTs or cohort studies.

7 SAFETY (SAF)

7.1 Research questions

Element ID	Research question
C0008	How safe is the use of 3D printed implants and cutting guides in relation to standard implants and cutting guides?
C0004	How does the frequency or severity of harm change over time or in different settings?
C0005	What are the susceptible patient groups that are more likely to be harmed through the use of 3D printed implants and cutting guides?
B0010	What kind of data/records and/or registry is needed to monitor the use of 3D printed implants and cutting guides and standard implants and cutting guides?

7.2 Results

Included studies

This domain included all studies from the EFF domain as well as three additional studies reporting safety concerns in maxillofacial and cranial surgery (61-63). Other safety issues not covered in these studies may exist as short and not long-term outcomes were generally examined.

Patient safety

[C0008] – How safe is the use of 3D printed implants and cutting guides in relation to standard implants and cutting guides?

Knee surgery

Few of the included studies included data on complications occurring in TKA comparing those undergoing patient-specific instruments (PSIs), patient-matched positioning guides (PMPGs), and navigation templates (NTs) and those using standard interventions. In these short-term studies, no additional complications associated with 3D printed implants and cutting guides in TKA were reported. In Huijbregts et al. (49), some of the most frequent complications were infection (10.1% vs. 10.9%), manipulation under anaesthetic (1.4% vs. 7.8%), venous thromboembolism (0% vs. 1.6%) and haemarthrosis (1.4% vs. 0%) in the PSI group compared with the standard instrumentation group, respectively. In Boonen et al. (50), some of the most frequent complications were infection (0% vs. 1.2%), manipulation under anaesthetic (4.9% vs. 2.5%), venous thromboembolism (1.2% vs. 0%) and haemarthrosis (2.4% vs. 0%) in the PMPG group compared with standard instrumentation. In Zhang et al. (54), there was no difference in infection or venous thromboembolism in the NT group compared with the standard intramedullary positioning group.

Maxillofacial surgery

One study examined complications in mandibular reconstruction comparing those assigned to computer-assisted mandibular reconstruction and those assigned to standard reconstruction. In Ayoub et al. (19), there was no significant difference in complication rate such as operating time or duration in the intensive care unit between the computer-assisted group and the standard group. However, there was a difference in ischaemic time, with a decrease in the computer-assisted group. Two retrospective studies of small sample size which were not included in the

EFF domain evaluated operating times between 3D printing groups (5.5 ± 0.5 hours) and standard groups (6.5 ± 0.7 hours) and found significant differences (61).

Cranial surgery

Chrzan et al. (63) examined complication rates in cranioplasty between those undergoing computer-aided design (CAD) modelling and those undergoing standard cranioplasty. There was a significant difference in mean operating time between the CAD group (120.3 minutes, 95% CI 110-140) and the control group (136.5 minutes, 95% CI 120-150; p<0.000004). In a study not included in the EFF domain, only complications from standard cranioplasty were evaluated. The most frequently observed complications were wound infection (11.3%), bone resorption (6.5%), or sunken bone plates (1.6%).

[C0004] – How does the frequency or severity of harm change over time or in different settings?

Knee, maxillofacial surgery, or cranial surgery

The included studies had some data on short-term outcomes in hospital settings but no information on long-term complications to examine safety outcomes such as implant survival. Therefore, it is not possible to further evaluate harm changes over time or to evaluate harm increases or decreases in different organisational settings such as implant failure, prosthesis problems, and continuing pain.

[C0005] – What are the susceptible patient groups that are more likely to be harmed through the use of 3D printed implants and cutting guides?

Knee, maxillofacial surgery or cranial surgery

3D printed implants and cutting guides in TKA are not recommended in patients with previous knee replacement of the same knee. Caution should be exerted in patients with any metal device that affects image quality of the knee, angular deformities greater than 15° of fixed varus, valgus, or flexion, tibial slope exceeding 15°, or with moderate to severe bony deformities, Charcot knee, or patients with severe patella tendon calcification that may prevent patella eversion[8]. No information is available concerning susceptible patient groups in mandibular reconstruction and cranioplasty.

***[B0010] - What kind of data/records and/or registry is needed to monitor the use of 3D printed implants and cutting guides and** standard **implants and cutting guides*?**

Knee, maxillofacial surgery or cranial surgery

In the developmental phase, the use of high-risk 3D-printed medical devices would only be allowed in a selection of specialist centres (phase I and D). This is to avoid having high-risk medical devices widely adopted in many hospitals without a thorough evaluation of their safety and added value. Before an innovation becomes widespread, a formal scientific evaluation should have taken place within an appropriate study design in which a comparison is made with existing alternatives (phase A). The government can (co-)finance a system to use existing administrative databanks.

8 [http://synthes.vo.llnwd.net/o16/LLNWMB8/INT%20Mobile/Synthes%20International/Product%20Support%20Material/legacy_DePuy_PDFs/DSUS-JRC-0115-0698-1_LR.pdf]

The producer should first finance a study to evaluate outcomes that are not present in the administrative databanks (such as comparative effectiveness in QoL) (3).

Regarding long-term performance, all new procedures must be reported to a follow-up database/ registry to provide data on complication rates of 3D printed implants and cutting guides in TKA compared with standard instrumentation group(s).

8 DISCUSSION

Description of technology and comparators

The Belgian Health Care Knowledge Centre's (KCE) health technology assessment on 3D printing applications for medical purposes (3) describes the regulation of medical devices for healthcare use and classifies different products according to their interaction with the human body from Class I to Class III. However, if the device falls under the definition of custom-made and not customisable, noting that the requirements for custom-made devices are less stringent, there is a risk of devices being commercialised without, for example, going through at least a CE mark process.

While a 3D printed prosthetic may be classified as Class I, or low risk, the technology has progressed sufficiently to produce more advanced implants and tools that would be defined as Class III, or high risk, medical devices; for example, surgical instruments, umbilical cord clamps for disaster relief efforts, and new implantable medical devices to help heal fractured bones, as in this assessment.

If such devices are mass produced on a 3D printer, then high-level, third-party oversight of safety, quality, and performance are mandatory. In Europe, that role is covered by CE mark notified bodies that certify market access. However, if the device falls under the custom-made definition, third-party oversight does not apply.

Devices produced via a standard process and then adapted to the specific features of the patient are considered "custom-made" under the Medical Devices Directives (guidelines relating to the application of the Council Directive 90/385/EEC on active implantable medical devices and the Council Directive 93/42/EEC on medical devices (https://ec.europa.eu/growth/single-market/european-standards/harmonised-standards/implantable-medical-devices_en). Historically this made sense, as custom-made items were typically low risk and few in number. However, as the number and complexity of custom-made devices has grown and become routine practice, health systems and regulators must ensure that they are subject to the same high-level scrutiny as mass-produced devices. New regulations should consider these aspects to ensure that the principles of ensuring safety and liability are secured.

These issues pose another challenge to health authorities with regard to safety. Although the final directive has not been published, different proposals have been made such as: "…the assembly or adaptation must be in accordance with validated instructions provided by the manufacturer of the device to be adapted; and that, if an individual modifies a device … in such a way that compliance with the essential principles may be affected, they shall assume the obligations incumbent on manufacturers". In this sense, the liability principle should be considered in order to trace who should be responsible for any damage caused by defects in the final product or its use.

This goes some way towards fixing the problem of responsibility and response. If health providers were to print devices for their patients by strictly following instructions from the supplier, they would not be considered the manufacturer under this change. However, there are still challenges to identifying who is responsible for the device.

Traditional definitions of manufacturer do not encompass the process of 3D printing custom-made implants and cutting guides. Generally speaking, it is assumed that the manufacturer who designs an item will manufacture that item. This is not always the case with the democratisation of 3D printing technology and the production of some medical devices.

Nevertheless, the directive is clear that all the producers involved in the production process are liable as well as all actors in the supply chain.

Health problem

3D printed medical devices are most frequently applied to knee, maxillofacial, and cranial surgery. The most frequent diseases in the included studies were primarily knee OA and secondary RA treated with TKA, oral cancer treated with mandibular reconstruction, and traumatic brain injury with intracranial hypertension treated with decompressive craniectomy and later cranioplasty. These are serious and global conditions, with oral cancer affecting over 300,000 people and TBI over 10 million people each year, and approximately 1% of the population make contact with a doctor with symptoms of knee arthritis (45,46). The introduction of 3D print technology does not significantly change standard instrumentation procedures in TKA, mandibular reconstruction, or cranioplasty but it may improve outcomes. In Europe, 3D print technology only accounts for ~1.3% of the 1,324,000 annual TKAs (1,2). In mandibular reconstruction and cranioplasty, there are no published data on the utilisation of the technologies in Europe, but 3D print technology is also growing in these clinical areas.

Clinical effectiveness

Thirteen studies reported on the use of surgical interventions using 3D print technology compared with standard interventions on patients undergoing knee, maxillofacial, or cranioplastic surgery. This assessment provided both a meta-analysis and a narrative summary on outcomes when meta-analysis was not possible. Overall, the evidence level for the included studies was very low to moderate, mainly due to the risk of bias and the imprecision of the estimates in the included studies, which might limit the robustness of our findings.

Results by outcome

Alignment

This outcome was only reported in patients undergoing TKA.

Number of outliers (by >3°) in TKA

The number of outliers in relation to TKA was reported in six RCTs and one SR with respect to five separate outcomes: hip-knee-ankle angle (limb), coronal femoral angle, coronal tibial angle, tibial slope, and femoral rotation. Results from the meta-analysis and SR are presented in Table 8.1.

Table 8.1: Meta-analysis regarding alignment in 3D surgery vs. standard. Results from RCTs and SRs (Thienpont et al. (55))

Endpoints	Results (OR)	P-value	Results SR* (RR)
Hip-knee-ankle angle	0.29 in favour of 3D print	<0.0001	0.79 in favour of 3D print (p=0.013)
Coronal femur	0.24 in favour of 3D print	<0.001	0.74 in favour of 3D print (p=0.043)
Coronal tibial	0.29 in favour of 3D print	0.005	1.30 (p=0.13)
Tibial slope	0.55	0.57	1.32 in favour of standard (p=0.001)
Femoral rotation	0.33	0.16	0.97 (p=0.88)

Operating time

In patients undergoing knee surgery, only minor differences in operating time were observed; however, differences were statistically significant, favouring 3D surgery patients compared with standard instrumentation. Estimates ranged from 4.4 to 10.7 minutes. The quality of the evidence was low and heterogeneity was high. No difference in overall operating time was found in maxilla-facial patients. A significant difference of 16.2 minutes was found in one small study of cranioplasty patients favouring 3D surgery (very low quality of evidence).

Other outcomes

No significant or clinically relevant differences were found in pain scores and blood loss. In relation to function and activities of daily living, no differences in the two groups were found in knee scores between patients undergoing knee reconstruction. Only one of three health-related quality of life scores showed a significant difference in favour of the intervention group.

In summary, 3D surgery using 3D printed implants and cutting guides in TKA compared with standard instrumentation resulted in greater precision, as demonstrated through outcomes such as malalignment (hip-knee-ankle angle, coronal femoral angle, and coronal tibial angle) or absolute deviation. No other outcomes showed clinical or statistically significant results in favour of 3D surgery or standard surgery. Until further evidence is generated, these results may support the use of 3D print technology as an alternative to standard surgery, with the caveat that the quality of current evidence varies from very low to low. Use should be restricted to reference centres, and data on safety and efficacy must be collected. Patients should be informed about alternatives, possible benefits, and the risks. Earlier studies also support the use of 3D surgery until additional high-quality studies are produced (1). However, it is necessary to establish what if any relevant improvements 3D printed surgery offers before any final decision is made on continuing use of the technology. Proposed data collection systems by EUnetHTA JA3, WP5 offer a good starting point to standardise evidence generation while ensuring quality.

Based on the available literature, it is challenging to weigh which outcomes/results are most important. From a patient perspective, patient-related outcomes such as functionality, QoL, and changes in sensory function seem to be most relevant. Unfortunately, it may be difficult to comment on these effects on the basis of the literature, since these results are not particularly well quantified or established. It should also be mentioned that it is often not possible to determine which differences in effect sizes are clinically relevant when comparing groups. The outcomes suggestive of a relevant effect (alignment) are proxy outcomes, such that direct patient effects such as pain or QoL are not immediate, although larger alignment problems in TKA patients may result in functional difficulties. It has been shown that between 6 and 12% of TKAs fail as a result of malalignment of the components (49), and since malalignment may contribute to instability, aseptic loosening, and unexplained pain (49), precision in these procedures is of great importance. As in this assessment and most studies concerning TKA patients, precision is demonstrated through outcomes such as outliers (often defined as a deviation by >3° from the planned positioning of the implant) or absolute deviation in degrees. In support of this approach, Gan et al. (52) commented that biomechanics research has demonstrated that precisely restoring the lower extremity can be a very effective method to avoid polyethylene wear. The same authors also suggested that increased contact pressure will lead to increased polyethylene wear, prosthesis loosening, and TKA failure. Gan et al. (52) also reported 3° varus–valgus alignment of the lower limb in the frontal plane to be optimal, and Pfitzner et al. (51) pointed out that in the absence of long-term studies, a neutral mechanical axis remains the gold standard. However, Huijbrechts et al. (49) said: "Future correlation with aseptic loosening is required to determine if the cumulative

deviation has clinical rather than mathematical value", and Thienpont et al. (55) said that "authors have concluded that the impact of mechanical coronal plane malalignment may be smaller than originally believed which may cast doubt on the premise of PSI". Future studies will need to demonstrate a relevant long-term impact of malalignment in TKA patients. Furthermore, it is important to note that the above results reflect the use of different 3D systems (Table 4.4, Table A1, Table A.2) and imaging modalities (MR and CT) and that intra- and inter-observer variability may influence alignment measurements (49).

Safety

Safety issues related to 3D print technology and standard instrumentation were examined in few of the included studies. There was no overall difference in complications between the technologies in TKA, mandibular reconstruction, or cranioplasty. A difference was found in ischaemic time in mandibular reconstruction, with a decrease in the 3D print group using individual surgical guides. The included studies only included data on short-term outcomes such as infection, venous thromboembolism, haemarthrosis, ischaemia, and operating time. Long-term complications such as harm change over time, implant failure, prosthesis problems, and continued pain are needed to fully evaluate which safety issues are relevant to this new technology (51,52,58). Another concern not accounted for is the associated exposure to ionising radiation triggered by the repeat CT-scans acquired in many of the 3D print technologies. Although the risk for any person is small, the increased exposure to radiation when using 3D print technology is not negligible (64).

Need for research/evidence gaps

Well-prepared RCTs or prospective cohort studies with relevant comparisons in all areas of 3D print technology are required. Accordingly, there is still a need to illustrate whether or not the effects and complications of 3D print technology are different to standard surgery. Also, future studies need to better utilise standardised assessment tools and gold-standard assessments and explicitly present criteria when necessary in alignment studies. Furthermore, it will be relevant to assess patient-related outcomes such as functional outcomes and QoL as well as long-term outcomes and complications such as implant survival and persistent pain. There also needs to be a focus on evaluation methods for 3D print technologies. The availability of CT and MRI and the recent developments in CAD software provide opportunities to update the evaluation methods for 3D printing technologies and thereby deliver more reliable and accurate results.

Another strategy for collecting information about the use of 3D printed implants and cutting guides could be to limit the use of 3D technology to a limited number of hospitals acting as reference centres. This offers a number of advantages, including better patient outcomes through concentrated expertise and, for devices without evidence of efficacy, opportunities for data collection.

9 CONCLUSION

3D printed technology showed greater precision in terms of malalignment than standard instrumentation in TKA. However, the evidence was of very low or low quality. No firm conclusions can be drawn for mandibular reconstruction and cranioplasty, since no other outcomes showed clinical or statistically significant results in favour of either technology. The clinical implications of the findings in TKA are uncertain, and further research is needed to assess patient-related outcomes from the use of 3D print technology before any final decision on continued use of the technology. Regarding safety, while a few short-term outcomes such as infection, venous thromboembolism, and haemarthrosis were reported, there were no overall differences except from ischaemic time in mandibular reconstruction between the assessed technologies.

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APPENDIX 1: METHODS AND DESCRIPTION OF THE EVIDENCE USED

Documentation of the Search Strategies

PubMed - primary studies:

- Date: 03/04/2018

- ID Search
- #1 Printing, Three-Dimensional, [Mesh]
- #2 Stereolithography, [Mesh]
- #3 Computer-Aided Design, [Mesh]
- #4 #1 OR #2 OR #3
- #5 “rapid prototyping”
- #6 “patient specific instruments”
- #7 “Patient specific instrument”
- #8 “Patient specific implant”
- #9 “Patient specific implants”
- #10 “Surgical guide”
- #11 “Surgical guides”
- #12 “Additive manufacturing”
- #13 “Medical additive manufacturing”
- #14 “Subtractive manufacturing”
- #15 “Computer numerical machine”
- #16 “3d printing”
- #17 “Three dimensional printing”
- #18 “3d-printing”
- #19 “three-dimensional printing”
- #20 #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19
- #21 #20 AND (Controlled Clinical trail [ptyp] OR Observational study [ptyp] OR Randomized Controlled trail [ptyp])

- #22 #21 AND last 10 years [PDat]
- #23 #22 AND Humans [Mesh]

PubMed – Reviews

- Date: 06/04/2018

- ID Search
- #1 Printing, Three-Dimensional, [Mesh]
- #2 Stereolithography, [Mesh]
- #3 Computer-Aided Design, [Mesh]
- #4 #1 OR #2 OR #3
- #5 “rapid prototyping”
- #6 “patient specific instruments”
- #7 “Patient specific instrument”
- #8 “Patient specific implant”
- #9 “Patient specific implants”
- #10 “Surgical guide”
- #11 “Surgical guides”
- #12 “Additive manufacturing”
- #13 “Medical additive manufacturing”
- #14 “subtractive manufacturing”
- #15 “Computer numerical machine”
- #16 “3d printing”
- #17 “Three dimensional printing”
- #18 “3d-printing”
- #19 “three-dimensional printing”
- #20 #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19
- #21 #20 AND (Systematic Reviews [ptyp] OR Meta-Analysis[ptyp])
- #22 #21 AND last 5 years [PDat]
- #23 #22 AND Humans [Mesh]

EMBASE – Primary studies

- Date: 06/04/2018

- ID Search
- #1 Three dimensional printing/exp
- #2 Stereolithography/exp
- #3 Computer aided design/exp
- #4 #1 OR #2 OR #3
- #5 “rapid prototyping”
- #6 “patient specific instruments”
- #7 “Patient specific instrument”
- #8 “Patient specific implant”
- #9 “Patient specific implants”
- #10 “Surgical guide”
- #11 “Surgical guides”
- #12 “Additive manufacturing”
- #13 “Medical additive manufacturing”
- #14 “subtractive manufacturing”
- #15 “Computer numerical machine”
- #16 “3d printing”
- #17 “Three dimensional printing”
- #18 “3d-printing”
- #19 “three-dimensional printing”
- #20 #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19
- #21 #20 AND ([controlled clinical trail]/lim OR [randomized controlled trail]/lim)
- #22 [2008-2018]/py
- #23 #22 AND [Humans]/lim

EMBASE – Reviews

- Date: 06/04/2018

- ID Search
- #1 Three dimensional printing/exp
- #2 Stereolithography/exp
- #3 Computer aided design/exp
- #4 #1 OR #2 OR #3
- #5 “rapid prototyping”
- #6 “patient specific instruments”
- #7 “Patient specific instrument”
- #8 “Patient specific implant”
- #9 “Patient specific implants”
- #10 “Surgical guide”
- #11 “Surgical guides”
- #12 “Additive manufacturing”
- #13 “Medical additive manufacturing”
- #14 “subtractive manufacturing”
- #15 “Computer numerical machine”
- #16 “3d printing”
- #17 “Three dimensional printing”
- #18 “3d-printing”
- #19 “three-dimensional printing”
- #20 #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19
- #21 #20 AND ([systematic review]/lim OR [meta analysis]/lim)
- #22 [2013-2018]/py
- #23 #22 AND [Humans]/lim

- **Cochrane**
- Date: 06/04/2018

- ID Search
- #1 MeSH descriptor: [Printing, Three-Dimensional] explode all trees
- #2 MeSH descriptor: [Stereolithography] explode all trees
- #3 MeSH descriptor: [Computer-Aided Design] explode all trees
- #4 #1 or #2 or #3 Publication Year from 2008 to 2018
- #5 "rapid prototyping" Publication
- #6 "patient specific instruments"
- #7 "patient specific instrument"
- #8 "patient specific implants"
- #9 "patient specific implant"
- #10 "Surgical guides"
- #11 "Surgical guide"
- #12 "additive manufacturing"
- #13 "medical additive manufacturing"
- #14 "subtractive manufacturing"
- #15 "computer numerical machine"
- #16 "3d printing"
- #17 "Three dimensional printing"
- #18 "3d-printing"
- #19 "Three-dimensional printing"
- #20 #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19
- #21 #4 or #20 Publication Year from 2008 to 2018
-
- A search on on-going clinical trials has been performed on ClinicalTrails.gov and Clinicaltrailsregister.eu. In both databases the search word was 3D. The search was performed the 19th of February 2018.

Evidence tables of individual studies included for clinical effectiveness and safety

Table A.1: Characteristics and extraction table of randomised controlled studies

Authors and year	Study type	Number of patients/ patient characteristics	Intervention(s) vs. comparison(s) and characteristics	Main endpoint(s)	Results
Huijbregts et al., 2016	RCT	140 knees in patients with end-stage rheumatoid or osteoarthritis (75 in PSI group with mean age of 66.7 and 65 in standard group with mean age of 69.0)	**Intervention:** PSI **Comparator:** Standard instrumentation **Application type:** TKA **Anatomic location of implant**: Knee **Description of the surgical procedure:** Medial parapatellar approach with implanting a cemented knee arthroplasty and patellar resurfacing when necessary **Material of 3D printed device:** No information **Type of printer used:** No information **Software used:** No information **PSI imaging modality:** MRI **PSI System:** Visionaire® **PSI Implant:** Legion systems or Genesis II **Standard implant:** Legion systems or Genesis II	Accuracy of component positioning and alignment in TKA Operating time, rate of early complications, OKS, and SF-12 scores. **Measurement tools:** Radiographs, CT scans and questionnaires **Length of follow-up:** 1 year **Loss to follow-up:** n=2 in PSI group and n=1 in standard group	**Outliers >3^0 deviation from planned alignment:** Hip Knee Ankle-angle (limb): ND Coronal femur: ND Coronal tibia: ND Tibial slope: Significant different in favour of standard care with 13% vs .20% outliers (p= 0.032) Femoral rotation: ND **Operating time:** ND **OKS:** ND **Physical and mental SF-12:** ND
Boonen et al., 2016	Multicentre, double-blind RCT	180 patients with knee osteoarthritis (90 in PMPG group with mean age of 69 and 90 in the standard group with mean age of 65)	**Intervention:** PMPG **Comparator**: Standard instrumentation. **Application type:** TKA **Anatomic location of implant:** Knee **Description of the surgical procedure**: Medial parapatellar approach with implanting a cemented knee arthroplasty and patellar resurfacing where necessary. **Material of 3D printed device**: No information **Type of printer used:** No information **Software used:** Materialise NV, Leuven, Belgium **PMPG imaging modality:** MRI **PMPG System:** Signature **PMPG Implant**: Vanguard **Standard implant**: No information	KSS, OKS, WOMAC, VAS, EQ-5D-3L index score, EQ-5D-3L VAS health and rate of complications **Measurement tools:** Questionnaires **Mean follow-up:** 44 months **Loss to follow-up:** n=8 in PMPG group and 9 in the standard group	**KSS:** ND **OKS:** ND **WOMAC**: ND **VAS:** ND **EQ-5D:** ND **EQ-5D VAS**: ND

Authors and year	Study type	Number of patients/ patient characteristics	Intervention(s) vs. comparison(s) and characteristics	Main endpoint(s)	Results
Pfitzner et al., 2014	RCT	90 patients with primary knee osteoarthritis (30 in CT-based PSI group with a mean age of 63, 30 in the MRI-based PSI group with a mean age of 65, and 30 in the standard instrumentation group with a mean age of 64)	**Intervention:** CT- or MRI-based PSI **Comparator:** Standard instrumentation **Application type:** TKA **Anatomic location of implant:** Knee **Description of the surgical procedure:** Posterior stabilized cemented TKA **Material of 3D printed device:** No information **Type of printer used**: No information **Software used:** No information **PSI imaging modality:** CT or MRI **CT-based PSI System:** TruMatch® **CT-based PSI Implant:** Sigma® (Press-fit condylar) **MRI-based PSI System:** Visionaire® **MRI-based PSI Implant:** Journey® **Standard implant:** Journey®	Accuracy of component positioning and alignment in TKA KSS, WOMAC, and operating time **Measurement tools:** Long leg radiographs, CT scans **and questionnaires** **Mean follow-up time:** 3 months **Loss to follow-up:** None	**Outliers >3^0 deviation from planned alignment:** Hip Knee Ankle-angle (limb): CT-based group: ND MRI-based group: Significant different in favour of PSI with 7% vs. 43% outliers (p= 0.002) Coronal femur: ND in both groups Coronal tibia: ND in both groups Tibial slope: ND in both groups Femoral rotation: CT-based group: Significant different in favour of PSI with 13% vs 50% outliers (p= 0.01) MRI-based group: ND **Operating time**: CT-based group: Significant different in favour of PSI with 63 min vs. 76 min (p< 0.001) MRI-based group: Significant different in favour of PSI with 58 min vs. 76 min (p< 0.001) **KSS:** No difference **WOMAC:** No difference
Gan et al., 2015	RCT	70 patients with serious knee osteoarthritis (35 in the NT group with mean age of 68.5, and 35 in the standard group with mean age of 67.8)	**Intervention:** Patient-specific navigational template **Comparator:** Standard instrumentation **Application type:** TKA **Anatomic location of implant:** Knee **Description of the surgical procedure:** Medial parapatellar approach with patellar eversion. **Material of 3D printed device:** Acrylate resin **Type of printer used:** Stereolithography, a rapid prototyping technique (Hen Tong Company, China) **Software used:** Materialise NV, Leuven, Belgium Imaging modality: CT **NT System**: No information **NT implant:** Scorpio Posterior Stabilized System **Standard implant:** Scorpio Posterior Stabilized System	Accuracy of component positioning and alignment in TKA Operating time and degree of blood loss. **Loss to follow-up:** None	**Outliers >3^0 deviation from planned alignment:** Hip Knee Ankle-angle (limb): Significant different in favour of NT group with 1 vs. 8 outliers (p< 0.001) Coronal femur: Significant different in favour of NT group with 1 vs. 9 outliers (p< 0.001) Coronal tibia: Significant different in favour of NT group with 1 vs. 10 outliers (p< 0.001) **Operating time:** Significant different in favour of NT group with 63 min vs. 76 min (p< 0.001) **Blood loss:** Significant different in favour of NT group with 200 ml vs. 290 ml (p< 0.001)

Authors and year	Study type	Number of patients/ patient characteristics	Intervention(s) vs. comparison(s) and characteristics	Main endpoint(s)	Results
Qiu et al., 2017	RCT	26 patients with end-stage knee osteoarthritis (10 in PSI group with mean age of 67.6 and 16 in the standard instrumentation group with mean age of 65.5)	**Intervention:** PSI **Comparator:** Standard instrumentation group. **Application type:** TKA **Anatomic location of implant:** Knee **Description of the surgical procedure:** Medial parapatellar approach with implanting a cemented knee arthroplasty and patellar resurfacing where necessary. **Material of 3D printed device:** No information Type of printer used: No information **Software used:** Arigin 3D Surgical Templating **Imaging modality:** CT **PSI System:** Arigin 3D Surgical Templating **PSI Implant**: No information **Standard implant**: No information	Accuracy of component positioning and alignment in TKA	**Deviation from planned alignment:** Hip Knee Ankle-angle (limb): Significant different in favour of PSI with 0.77^0 vs. 3.13^0 ($p< 0.05$) Coronal femur: Significant different in favour of PSI with 0.37^0 vs. 2.35^0 ($p< 0.05$) Coronal tibia: Significant different in favour of PSI with 0.11^0 vs. 1.09^0 ($p< 0.05$)
Zhang el. at., 2016	Single-blind RCT	40 patients with knee osteoarthritis (20 in the NT-group with mean age of 63, and 20 in the standard intramedullary positioning group with mean age of 62.1)	**Intervention:** NT **Comparator:** Standard intramedullary positioning **Application type:** TKA **Anatomic location of implant:** Knee **Description of the surgical procedure:** No information **Material of 3D printed device**: No information **Type of printer used:** SPSS 350B solid laser rapid prototyping machine (Shanxi Hengtong Intelligent Machine Co., China) **Software used:** Imageware 12.0 **Imaging modality**: CT **NT System:** No information **NT implant**: Triathlon **Standard implant:** Triathlon	Accuracy of component positioning and alignment in TKA Operating time, intraoperative haemorrhage volume **Follow-up time:** 12 months **Loss to follow-up**: : n=2 in NT group and 2 in CIP group	**Deviation from planned alignment:** Hip Knee Ankle-angle (limb) : Significant different in favour of NT group with 0.6^0 vs 2.7 ($p= 0.0435$) Sagittal femoral: ND Coronal tibia: Significant different in favour of NT group with 0.7^0 vs. 1.9 ($p= 0.0456$) **Operating time:** Significant different in favour of NT group with 46.8 min vs. 57.5 min ($p= 0.0086$) **Blood loss:** ND

Authors and year	Study type	Number of patients/ patient characteristics	Intervention(s) vs. comparison(s) and characteristics	Main endpoint(s)	Results
Brandão et al., 2016	Single-centre, double-blind RCT	40 patients (22 in surgical guide group and 18 in control group) with median age of 43.5 requiring mandibular reconstruction	**Intervention:** Surgical guides **Comparator:** Standard surgery **Application type:** Mandibular reconstruction **Anatomic location of implant:** Mandible **Description of the surgical procedure:** No information **Material of 3D printed device:** Acrylic resin **Type of printer used:** No information **Software used:** No information **Imaging modality:** CT **Surgical guide:** Custom made **Standard surgery:** Without surgical guides	Occlusion pattern and stability Opening deviation Maxillomandibular relationship Loss of prosthetic space Esthetic preparation Diet, speech, oral competence and QoL **Length of follow-up:** 18 months **Loss to follow-up:** 4 patients Measurement tools: Clinical examination, CT scans and questionnaires	**Surgical guide group vs control group** **Occlusion pattern change**: Significant different in favour of surgical guide group with 0% vs. 66.7% (p= 0.032) **Occlusion stability:** ND **Opening deviation**: ND **Favourable maxillomandibular relationship:** Significant different in favour of surgical guide group with 77.3% vs. 44.4% (p= 0.035) **Loss of prosthetic space**: ND **Diet, speech and oral competence:** ND **QoL:** Significant different in favour of surgical guide group (p=0.027)
Ayoub et al., 2014	RCT	20 patients (10 in rapid prototyping group with mean age of 52.3 and 10 in control group with a mean age of 54.7) requiring mandibular reconstruction	**Intervention:** CAD and rapid prototyping of individually pre-operative adjusted cutting guide **Comparator:** Standard treatment **Application type:** Mandibular reconstruction **Anatomic location of implant**: Mandible **Description of the surgical procedure:** No information **Material of 3D printed device:** Polyamide **Type of printer used:** Laser sintering Software used: 3matic-Software, Materialise NV, Leuven, Belgium **Imaging modality:** CT **Surgical guides:** Custom made **Standard surgery:** Without surgical guides	Time for harvesting and shaping the transplant, reconstruction, osteosynthesis, ischemia and overall operating time Size of harvested bone ICU time Postoperative hospitalization time Blood transfusion Condyle position Intercondylar distance Transplant fail **Loss to follow-up:** None **Measurement tools**: Clinical examination and CT scan	**Rapid prototyping group vs. standard** **Time shaping donor site:** Significant different in favour of standard group with 37.8 min vs. 62.1 min (p< 0.005) **Time shaping defect site**: Significant different in favour of rapid prototyping group 6.2 min vs. 20.3 min (p<0.001) **Time for the osteosynthesis**: Significant different in favour of rapid prototyping group with 10.1 min vs. 18.2 min (p<0.005) Overall reconstruction time: Significant different in favour of rapid prototyping group with 16.4 min vs. 38.5 min (p<0.001) Ischemic time: Significant different in favour of rapid prototyping group with 96.1 min vs. 122.9 min (p<0.005) **Overall operating time:** ND **ICU time:** ND **Postoperative hospitalisation time**: ND **Blood transfusion:** ND **Intercondylar distance (pre- vs. post-surgery):** Significant different in favour of rapid prototyping group with 1.3mm vs. 5.5 mm (p<0.001)

Authors and year	Study type	Number of patients/ patient characteristics	Intervention(s) vs. comparison(s) and characteristics	Main endpoint(s)	Results
Al-Ahmad et al., 2013	Double-blind, RCT, split-mouth design	8 patients scheduled for bilateral sagittal split ramus osteotomy (SSRO) (8 sides in Computer-assisted SSRO group and 8 sides in the standard SSRO group) with a mean age of 23.	**Intervention:** Computer-assisted SSRO **Comparator**: Standard SSRO **Application type:** Mandibular SSRO **Anatomic location of implant:** Mandible **Description of the surgical procedure:** Obwegeser-Dal Pont technique **Material of 3D printed device**: Acrylic resin **Type of printer used**: ZCorp Z310 **Software used:** Solid Planner, Solid Model Co. **Imaging modality:** CT **Surgical guides:** Custom-made **Standard surgery**: Without surgical guides	On four cutaneous points: Tactile threshold, two-point discrimination and direction of brush stroke. Subjective changes in sensory function Intraoperative parameters assessed by surgeon **Length of follow-up**: 6 months **Measurement tools:** Semmes-Wein-stein monofilaments	**Computer-assisted SSRO vs.** standard **SSRO (time after surgery):** **Tactile threshold:** Significant different in favour of computer-assisted SSRO group with 67% abnormal threshold after 1 week at lower lip and chin vs. 83% abnormal threshold ($p< 0.05$). Significant difference also at the chin after 3 months and lower lip after 6 months. **Two-point discrimination:** Significant different in favour of computer-assisted SSRO group at lower lip at 1 week and chin at 6 months ($p< 0.05$). **Direction of brush stroke:** ND **Subjective changes in sensory function:** Significant different in favour of computer-assisted SSRO group at 1 week **Intraoperative parameters assessed by surgeon:** ND

Abbreviations: CT=Computerised tomography; EQ-5D-3L index score=EuroQol-5D-3L VAS health; FFC=Frontal femoral component angle; FTC=Frontal tibial component; HKA angle-Hip-Knee-Ankle angle; KSS=Knee Society Score; LTC=Lateral tibial component; ND=No difference; NT group=Navigation Template group; OKS=Oxford Knee Scores; PMPGs=Patient-matched positioning guides; PSI=Patient-specific instrumentation; RCT=Randomised controlled trial; SF-12=ShortForm-12 scores; TKA=Total knee arthroplasty; VAS=Visual analogue scale; WOMAC=Western Ontario and McMaster osteoarthritis index.

Table A.2: Characteristics and extraction table of other relevant studies

Authors and year	Study type	Number of patients/ patient characteristics	Intervention(s) vs. comparison(s) and characteristics	Main endpoint(s)	Results
Thienpont et al., 2017	Systematic Review and Meta-Analysis Search date: 2011 through 2015 Databases: PubMed and Embase Included studies: 44 (20 RCT and 24 cohorts)	5,822 knees (2,866 PSI group and 2,956 standard care group) Eligibility criteria: PSI and standard instrumentation compared, primary TKA, a least 1 of the study outcomes reported, English, French, German or Dutch language studies, follow-up >6 month	**Intervention:** PSI **Comparator:** Standard instrumentation **Application type:** TKA **Anatomic location of implant:** Knee **Description of the surgical procedure**: No information **Material of 3D printed device:** No information **Type of printer used:** No information **Software used:** No information **Imaging modality:** CT or MRI **PSI System:** Visionaire, Sinature, Zimmer PSI, TruMatch or MyKnee **PSI Implant:** No information **Standard implant:** No information	Malalignment coronal/sagittal (mechanical axis, tibia or femur) and KSS (knee and function) Operative time, tourniquet time, and blood loss	**PSI vs. standard (Relative risk of axis malalignment):** Mechanical axis: 0.79 (CI 0.65-0.95) p=0.013 Coronal tibia: ND Sagittal tibia: 1.32 (CI 1.12-1.56) p=0.001 Coronal femur: 0.74 (CI 0.55-0.99) p=0.043 Sagittal femur: ND **Operating time (mean difference in minutes):** -4.4 (CI -7.2- -1.7) p=0.002 **Blood loss**: (mean difference in ml): -37.9 (CI -68.4- -7.4) p=0.015 **Tourniquet time:** ND **KSS (Knee):** ND **KSS (Function) (mean difference):** 4.3 (CI 1.5-7.2) p=0.003
Mannan et al., 2016	Systematic Review and Meta-analysis Search date: 2000-2015 Databases: PubMed, Cochrane Collaboration Trial registry and library, MEDLINE and Embase Included studies: 8 (5 RCT´s and 3 prospective-comparative)	828 knees (418 in PSI group and 412 in standard instrumentation group) Inclusion criteria: Level of evidence 1 or 2, PSI and standard instrumentation compared ≥10 patients in each group, reporting mean and sd, and English language studies. Exclusion criteria: Fracture deformity, tumor, animal, cadaveric studies.	**Intervention:** PSI **Comparator**: Standard instrumentation **Application type:** TKA **Anatomic location of implant**: Knee **Description of the surgical procedure:** No information **Material of 3D printed device:** No information **Type of printer used:** No information **Software used:** No information **Imaging modality:** CT or MRI **PSI System:** Visionaire, TruMatch Sinature or MyKnee **PSI implant:** Genesis II, Nexgen, Press-fit condylar, Journey, Vanguard or GMK **Standard implant:** No information	Postoperative KSS (knee and function) and range of movement Postoperative OKS and WOMAC scores	**PSI vs. standard:** **KSS (Knee):** ND **KSS (Function):** ND **ROM:** ND **OKS:** ND **WOMAC:** ND

Authors and year	Study type	Number of patients/ patient characteristics	Intervention(s) vs. comparison(s) and characteristics	Main endpoint(s)	Results
Mazzoni et al., 2013	Prospective Comparative Study	12 oncology patients with tumor lesions (7 in prosthetically guided surgery group and 5 in control group) requiring mandibular reconstruction	**Intervention:** Prosthetically guided maxillofacial surgery to produce custom made guides and reconstructive plate **Comparator:** Standard reconstruction with indirect CAD/computer-aided manufacturing procedure **Application type:** Mandibular reconstruction **Anatomic location of implant:** Mandible **Description of the surgical procedure:** No information **Material of 3D printed device:** Cobolt-chrome-molybdenum (cutting guide) and Titanium (bone plate) **Type of printer used:** No information **Software used:** CMF-Software, version 6.0, Materialise, Leuven, **Belgium** **Imaging modality:** CT	Midline deviation (vertical and horizontal) Variation in planes of the mandibular angle Angular deviation of the mandibular arch Condyle position **Measurement tools:** Clinical examination and radiographs **Follow-up time:** 1 month	**Surgery accuracy evaluation test group vs control group :** Midline deviation (vertical and horizontal): ND Mandible angle-shift right: ND Mandible angle-shift left: Significant different in favour of test group with 1.4 mm vs. 5.042 mm (p< 0.006) Angular deviation of the mandibular arch: ND Condyle position right: Significant different in favour of test group with mean 1.297 mm vs..4.458 mm (p= 0.035) Condyle position left: ND
Chrzan et al., 2012	Prospective Comparative Study	39 patients (19 in rapid prototyping group at the age of 21-54 and 20 in control group at the age of 18-60) requiring cranioplasty	**Intervention:** CAD and rapid prototyping of individually pre-operative adjusted prosthesis **Comparator:** Standard instrumentation with manually adjusted prosthesis **Application type:** Cranioplasty **Anatomic location of implant:** Skull **Description of the surgical procedure:** No information Material of 3D printed device: Polypropylene-polyester or aluminium-silicon **Type of printer used:** Milling Arrow 500 **Software used:** CATIA (Dassault Systémes, Vélizy-Villacoublay, France) **Imaging modality:** CT **CAD implant:** Codubix **Standard implant**: Manually adjusted prosthesis	Operating time Surgeons opinion	**Rapid prototyping group vs. standard** **Operating time:** Significant different in favour of rapid prototyping group with 120.3 min vs. 136.5 min (p< 0.001)

Abbreviations: CT scans Computerised tomography, EQ-5D-3L index score EuroQol-5D-3L VAS health, FFC Frontal femoral component angle, FTC Frontal tibial component, HKA angle Hip-Knee-Ankle angle, KSS Knee Society Score, LTC Lateral tibial component, ND No difference, NT group Navigation Template, group OKS Oxford Knee Scores, PMPGs Patient-matched positioning guides, PSI Patient-specific instrumentation, RCT Randomised controlled trial, SF-12 ShortForm-12 scores, TKA Total knee arthroplasty, VAS Visual Analogue scale, WOMAC Western Ontario and McMaster osteoarthritis index.

List of on-going and planned studies

Table A.3: List of on-going studies with custom-made or customisable 3D printed implants and cutting guides for knee, maxillofacial or cranial surgery

Study Identifier	Estimated completion date	Study type	Number of patients	Intervention	Comparator	Patient population	Endpoints
NTC03292679 Craniofacial Applications of 3D printing	September 2019 Status: Not yet recruiting	RCT	60	Subjects that are randomised into Arm B will have custom models of relevant portions of their facial skeleton printed and used as templates for bending and shaping plates for stabilising the fracture(s).	Subjects that are randomized into Arm A will have their fractures repaired in the usual fashion i.e. using plates that are bent by free hand.	12 years and older (Child, Adult, Older Adult) Sex: All	Operative time
NCT03057223 Three-Dimensional Printing of Patient-Specific Titanium Plates in Jaw Surgery: A Pilot Study	July 2021 Status: Recruiting	Interventional no randomisation	48	3D-printed patient-specific titanium plates will be used in patients.	No comparator	18 years and older (Adult, Older Adult)	Intraoperative success rate Incidence of postoperative adverse events (Safety)
NCT02914431 Personalised Titanium Plates vs CAD/CAM Surgical Splints in Maxillary Repositioning of Orthognathic Surgery	December 2019 Status: Not yet recruiting	RCT	72	The cutting guides will be placed into the planned position. The 11 screw holes will be drilled using the predetermined screw holes on the guides. The osteotomy / ostectomy will then start. Next, the 3D printing personalised maxillary fixation plates will be adapted to reposition the Le Fort I segment to the planned position. The 11 screw holes on the bones defined by the cutting guides will be used again as the bony reference. The personalised plate will be first firmly installed on the maxilla above the osteotomy line by aligning the corresponding 5 screw holes on the plate to the bone. Afterwards, the osteotomised Le Fort I segment will be moved and rotated until all the remaining corresponding 6 screw holes on bone and plate are aligned.	After the LeFort I osteotomy, the intraoperative repositioning of the maxilla will be accomplished using CAD/CAM surgical splints and the fixation of the maxilla is accomplished using commercial titanium plates.	18 years to 35 years	Difference of the maxillary position Operative time Intraoperative blood loss Cost of treatment

Abbreviations: RCT=Randomised controlled trial; CAD: Computer-aided design; CAM=Computer-aided manufacturing

Table A.4: GRADE profile. 3D-print technology compared to standard instrumentation in knee surgery

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	3D-print technology	usual care	Relative (95% CI)	Absolute (95% CI)		
Hip-knee-ankle alignment (degrees)												
4	randomised trials	serious [a]	not serious	not serious	serious [d]	none	21/174 (12.1%)	44/145 (30.3%)	**OR 0.29** (CI 0.16-0.52)	**191 fewer per 1.000** (119-238)	⊕⊕◯◯ LOW	IMPORTANT
Absolute deviation in degrees												
2	randomised trials	very serious [a]	not serious	not serious	serious [d]	none	79	80	-	mean **1.28 degrees lower** (3.29-0.74)	⊕◯◯◯ VERY LOW	IMPORTANT
Operating time												
3	randomised trials	serious [b]	not serious	not serious	serious [d]	none	122	117	-	mean **9.47 minutes lower** (18.1-0.84)	⊕⊕◯◯ LOW	IMPORTANT
Oxford Knee Score (OKS) (1 year follow-up)												
2	randomised trials	serious [a]	not serious	not serious	not serious	none	148	141	-	mean **1.29 points higher** (0.84-3.41)	⊕⊕⊕◯ MODERATE	IMPORTANT
Knee Society function score (3 month follow-up)												
2	randomised trials	serious [a]	not serious	not serious	serious [d]	none	120	120	-	median **0** (0)	⊕⊕◯◯ LOW	IMPORTANT
Proportion of outliers (> 3°) - coronal femur												
4	randomised trials	serious [a]	not serious	not serious	serious [d]	none	10/174 (5.7%)	31/145 (21.4%)	**OR 0.24** (0.09-0.68)	**153 fewer per 1.000** (58-190)	⊕⊕◯◯ LOW	IMPORTANT

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**3D-print technology**	**usual care**	**Relative (95% CI)**	**Absolute (95% CI)**		
Proportion of outliers (> 3°) - coronal tibia												
4	randomised trials	serious [a]	not serious	not serious	serious [d]	none	9/174 (5.2%)	25/145 (17.2%)	**OR 0.29** (0.12-0.69)	**115 fewer per 1.000** (47-148)	⨁⨁◯◯ LOW	IMPORTANT
Proportion of outliers (> 3°) - tibial slope												
3	randomised trials	serious [a]	serious [c]	not serious	serious [d]	none	27/139 (19.4%)	23/110 (20.9%)	**OR 0.91** (0.50-1.66)	**15 fewer per 1.000** (92-96)	⨁◯◯◯ VERY LOW	

Abbreviations: CI=confidence interval; OR=odds ratio

Explanations a. Unclear risk of bias related to blinding in included studies. High risk of bias related to randomisation and allocation in study by Qui et al., 2017 b. Studies affected by unclear risk of bias in many domains. c. Down-graded to serious because of high heterogeneity between studies and confidence intervals of point estimates do not overlap. d. downgraded to serious because of broad confidence intervals.

Applicability tables

Table A.5: Summary table characterising the applicability of a body of studies

Domain	Description of applicability of evidence
Population	The target population for this assessment is adult patients (>18 years) undergoing knee, maxillofacial, or cranial surgery. The target population of this assessment did not differ from the population enrolled in the included studies. The most frequent diseases in the included studies are primarily knee osteoarthritis and secondary rheumatoid arthritis treated with total knee arthroplasty (TKA), oral cancer treated with mandibular reconstruction, and traumatic brain injury with intracranial increased pressure treated with decompressive craniectomy and later cranioplasty. Patients undergoing TKA were generally older than other patient groups.
Intervention	The technology described in this assessment is related to the use of 3D printers for the production of custom-made or customisable 3D printed implants and cutting guides for improving outcomes in patients undergoing knee, maxillofacial, or cranial surgery. The interventions in the included studies cover a wide range of 3D technologies concerning materials, printers, and software and different ways of combining these parts in the process.
Comparators	The comparator is standard produced implants and cutting guides which also reflect a variety of procedures not always well described in the included studies.
Outcomes	Effectiveness outcomes most frequently reported in the included studies were alignment and precision, but also functional outcomes were reported. Regarding safety issues, the follow-up period was often too short to report on durability/longevity in relation to 3D print technology.
Setting	The studies included enrolled patients in Germany, Brazil, China, Italy, Poland, Australia, England, Jordan, Switzerland, and The Netherlands in a hospital setting.

APPENDIX 2: CHECKLIST FOR POTENTIAL ETHICAL, ORGANISATIONAL, PATIENT AND SOCIAL AND LEGAL ASPECTS

1. Ethical	
1.1. Does the introduction of the new technology and its potential use/non-use instead of the defined, existing comparator(s) give rise to any new ethical issues?	Yes/No
1.2. Does comparing the new technology to the defined, existing comparators point to any differences that may be ethically relevant?	Yes/No
2. Organisational	
2.1. Does the introduction of the new technology and its potential use/non-use instead of the defined, existing comparator(s) require organisational changes?	Yes/No
Organisational changes are inevitable if one should decide to implement the use of 3D printed implants and surgical guides as a supplement to or as a replacement for standard implants and surgical guides. The whole process of creating data for image editing and producing the device will change and involve the hospital and the individual health professional in new ways. These changes will mainly consist of changes in work flow at the hospital department and changes in competences for the personal. The impact of these changes depends on the organisational scenario implemented. The use of 3D printed implants and surgical guides could be organised in many ways and with different consequences. • The implants and surgical guides could be printed locally in each department where they are used • The implants and surgical guides could be printed at each hospital in a central printing department and then distributed to local departments afterwards • The implants and surgical guides could be printed in a central printing department established by all hospitals in a region or a country • The implants and surgical guides could be printed by a private external manufacturer and send to the hospital departments afterwards. These manufacturers could both be national and international These different ways of organising the printing process for 3D printed implants and surgical guides will place different demands on the organisation, and there is a huge differences in the skills required in house. The different scenarios for organising the 3D printing process also come with different legal requirements. See the paragraph below.	
2.2. Does comparing the new technology to the defined, existing comparator(s) point to any differences that may be organisationally relevant?	Yes/No
See above (section 2.1)	
3. Social	
3.1. Does the introduction of the new technology and its potential use/non-use instead of the defined, existing comparator(s) give rise to any new social issues?	Yes/No
3.2. Does comparing the new technology to the defined, existing comparator(s) point to any differences that may be socially relevant?	Yes/No
4. Legal	
4.1. Does the introduction of the new technology and its potential use/non-use instead of the defined, existing comparator(s) give rise to any legal issues?	Yes/No
The following legal issues have been identified by KCE in their report on *"Responsible use of high-risk medical devices: The example of 3D printed medical devices"* (3) and may be relevant to address in this assessment as well. For a thorough discussion of more legal aspects of the issue, please see the above-mentioned report: • **Requirements for market access:** In the current EU regulations, the requirements for putting 3D printed medical devices on the market depends on their classification as a "standard", "customisable", or "custom-made" device. "Custom-made" devices are unique devices fitted to an individual patient, whereas "customisable" medical devices are devices that can be (mass) produced via a standard process and individualised according to individual parameters. Currently, customisable devices are regarded as prescription devices that are made once for a certain patient. As a consequence, they are usually classified with the custom-made devices. In contrast to "standard" medical devices, manufacturers of custom-made medical devices, regardless of the risk profile, do not need to apply any CE marking to their product, there are no specific quality system requirements and, for the higher risk classes, there is	

no prior external evaluation of the device by a notified body. Manufacturers do have to draw up a statement (Annex VIII MDD) with identification data and characteristics of the device, the identity of the patient (coded or not), the prescribing physician, and as applicable the hospital concerned. They must in addition declare that the essential requirements of Annex I MDD (among others, justification of material choice, biocompatibility requirements, and sterility requirements) are fulfilled. However, they need not demonstrate that the 3D printed device is safer or more effective than (possibly) existing alternatives. According to the new EU regulations, stricter requirements for 3D printed medical devices made in larger quantities will be imposed. This means that customisable medical devices will have to comply with the same conditions as standard medical devices for market access. An exception to the stricter legislation for standard medical devices was made for medical devices that are made in hospitals. Aside from the essential requirements of Annex I, the requirements of the Medical Devices Regulation (MDR) (among others, CE marking, assessment by a notified body for certain risk classes) are not applicable under a number of conditions. The new regulations took effect on May the 25th 2017 and will be directly applicable in spring 2020 for the MDR and spring 2022 for the *In Vitro* Diagnostics Regulation (IVDR). Thus, based on the above, there are currently (and in the future) different legal requirements between the different types of 3D printed medical devices and between 3D printed medical devices and the comparators (standard medical devices).

- **Liability:** According to the principles of product liability, the producer is liable for any defect in its product. In 3D printing, however, there is a deviation from the traditional chain of production, distribution and use. Who is the producer here? Many parties are involved in the production of 3D devices: the surgeon who makes the initial design, the software engineer who develops the 3D design, the producers of the 3D printer, material, software, and implant, the implanting surgeon, the hospital, etc. The Product Liability Directive (PLD)[9] states that member states 'must impose strict liability on' producers when their products are defective and cause bodily injury, without the need for the victim to demonstrate that the producer has committed an error. The PLD also encompasses all medical devices that are made in the EU or imported. This strict liability is however only applicable to 'industrially made products'. It has not yet been determined by the EU whether 3D printed medical devices fall under this PLD, and no EU case law yet exists on the concept 'industrially produced'.
- **Protection of person data:** The 3D printing process unavoidably also involves the processing of health data of the individual patient. In addition, these data can be used for other than therapeutic purposes, e.g. for scientific research or reimbursement purposes (see below). Privacy legislation protects the processing of personal data and has developed rules for this.[10] It is very important to know who is regarded as "responsible for processing" by law. This person is in fact charged with almost all the legal obligations to guarantee protection of the processed data. Hospitals will generally be regarded as responsible for processing the personal data of the patient required for the 3D printing process. If hospitals outsource 3D printing to an external producer, they will have to conclude a processing agreement with it. If the conditions of the privacy legislation are met, no specific problems arise in 3D printing.
- **Patients' rights:** Patients have the right to be properly informed about alternatives. This could be an issue if only one alternative is reimbursed in the health care system.

4.2. Does comparing the new technology to the defined, existing comparator(s) point to any differences that may be legally relevant?	Yes/No
See above (section 4.1)	

[9] Council Directive 85/374/EEC of 25 July 1985 on the approximation of the laws, regulations and administrative provisions of the Member States concerning liability for defective products, PB L 210 of 7/8/1985, pp. 29–33.

[10] EU: Directive 95/46/EC of the European Parliament and of the Council of 24 October 1995 on the protection of individuals with regard to the processing of personal data and on the free movement of such data, PB L 281 of 23/11/1995 pp. 0031 - 0050 and Regulation (EU) 2016/679 of the European Parliament and of the Council of 27 April 2016 on the protection of natural persons with regard to the processing of personal data and on the free movement of such data, and repealing Directive 95/46/EC, PB L 119 of 4/5/2016, pp. 1–88; Belgium: Law of 8 December 1992 on the protection of privacy in relation to the processing of personal data, *Belgian Official Gazette*, 18 March 1992 and its implementation decrees.

APPENDIX 3: TEC DOMAIN - 3D PRINTERS FOR IMPLANTS AND CUTTING GUIDES

The technology

Additive manufacturing (AM), or 3D printing, can no longer be considered as a 'technique for prototyping'. Recent advances in AM have resulted in its application in several sectors including healthcare. AM offers the capacity to engineer complex topography into materials with specific chemical, physical, and mechanical properties.

This has allowed the production of personalised prosthesis, implants, and devices for medical applications. 3D printed medical implants and devices that are in clinical use today are constructed predominantly with metals, ceramics, and organic polymers.

Common types of 3D printers

The type of 3D printer chosen for an application often depends on the application to which the final product will be used, that also defines the materials to those printers use and how the layers in the finished product are bonded (15). Although a wide range of 3D printing systems have been developed for industrial use; stereolithography (SLA), multijet modelling (MJM), selective laser sintering (SLS), and fused deposition modelling (FDM) are the main approaches that have been explored for medical applications (65). They can also be classified into: a) resin-based systems; b) powder-based systems; c) extrusion-based systems; and d) droplet-based systems. Each technique differs in the manner in which layers are built and printing materials used. 3D bioprinting spans between laser-based, extrusion-based, and droplet-based systems. An overview of each printer technology is given below and summarised in Table A.6 (15,66).

Stereolithography (SLA). Resin-based systems

Amongst the photopolymerisation systems, stereolithography (SLA) was the first RP system known. In this process, a photopolymer is cured by a low-powder ultraviolet (UV) laser that solidifies specific areas on the surface of the liquid through a chain reaction initiated by reactive species generated by UV exposure. An SLA printer uses resin-based materials. Photocuring as a methodology for RP is particularly attractive for several reasons: high levels of build resolution, smooth part surfaces that do not typically require finishing processes, a good z axis strength due to chemical bonding between layers, fast builds possible, and the ability to print clear objects. Once the planar sections are completed, the prototype is then post-cured in a controlled furnace, or an ultraviolet curing apparatus, for a designated period of time, to allow final polymerisation (14).

MultiJet modelling (MJM). Droplet-based systems

Another cluster of 3D printing techniques includes droplet-based systems, where the liquid material is deposited in a droplet form instead of a continuous flow. The material often turns solid after deposition via cooling (e.g., by crystallisation or vitrification), chemical changes (e.g., through the cross-linking of a polymer), or solvent evaporation (67). In the MultiJet printing or PolyJet technology, the heads are placed on a jetting head that deposits tiny droplets of ultraviolet (UV)-curable resin onto the build tray. After building each layer, UV bulbs alongside the jetting head harden the layer, and the tray moves down in the z direction a certain distance so that the next layer can be printed (68). The main advantage of MJM techniques is the high resolution comparable with laser-based systems. However, printing materials used by jetting-based processes are limited and the high price of these printers make this technology more suitable for large-scale production.

Selective laser sintering (SLS). Powder-based systems

An SLS printer uses powdered material as the substrate for printing new objects. A laser draws the shape of the object in the powder, fusing it together. Then a new layer of powder is laid down and the process repeats, building each layer, one by one, to form the object. Laser sintering can be used to create metal, plastic, and ceramic objects. The degree of detail is limited only by the precision of the laser and the fineness of the powder, so it is possible to create especially detailed and delicate structures with this type of printer (15).

One of the major advantages of the SLS technology is the ability to process about any material in a powdered form: polymers, metals, ceramics, and a variety of composite materials such as glass reinforced polymers, metal/polymer composite, and metal/metal composites (69). Moreover, SLS does not require the use of organic solvents and can be used to make intricate biphasic scaffold geometries at both the macro and micro scale (70). These possibilities have opened the way for many medical applications, ranging from the fabrication of high-performance biomaterials such as HA-reinforced polyethylene composites for bioactive bone implants, to biodegradable polymers including polycaprolactone (PCL) (7,8,70) and poly-L-lactic acid (PLLA) (9) or nonbiodegradable polymers such as ultrahigh molecular weight polyethylene (UHMWPE) (10) and polyether ether ketone (PEEK) (71).

Other powder-based technologies include direct metal laser sintering (DMLS), selective laser melting (SLM), and direct laser forming (DLF), all of which use concepts comparable to the SLS except that the material is fully melted rather than sintered. Electron beam melting (EBM) is another powder-based system which differs from SLM only by the use of an electron beam as its power source instead of a high-power laser beam. DMLS and DLF has been investigated for the fabrication of porous titanium dental implants (67-69) (71-72) and Ti–6Al–4V scaffolds for bone tissue engineering and orthopaedic applications (73-75). The main disadvantages of SLS/SLM techniques are poor surface and dimensional accuracy, as well as low material properties that do not meet the prerequisite for industrial applications in terms of microstructure and mechanical strength. To address these drawbacks, post-processing treatments like depowdering, polishing, painting, heat-treatment, and furnace-infiltration can be employed (76). However, these steps are considered critical in direct RP for complex and controlled porous interconnected architectures (77).

Fused Deposition Modelling (FDM). Extrusion-based technology

Fuse deposition modelling (FDM) is a common material extrusion process and is trademarked by the company Stratasys (https://www.stratasys.com/). FDM is an affordable extrusion-based technology. A spool of thermoplastic filament feeds into an FDM extrusion head heated above the melting temperature of the material. FDM printers are much more common and inexpensive than the SLS type (12). An FDM printer uses a printhead similar to an inkjet printer (12). However, instead of ink, beads of heated plastic are released from the printhead as it moves, building the object in thin layers (12,15). This process is repeated over and over, allowing precise control of the amount and location of each deposit to shape each layer. Since the material is heated as it is extruded, it fuses or bonds to the layers below (15). As each layer of plastic cools, it hardens, gradually creating the solid object as the layers build. Depending on the complexity and cost of an FDM printer, it may have enhanced features such as multiple printheads (12). FDM printers can use a variety of plastics. In fact, 3D FDM printed parts are often made from the same thermoplastics that are used in traditional injection moulding or machining, so they have similar stability, durability, and mechanical properties (15).

Table A.6: 3D printing solutions and use

Technology	Best suited for
SLA	Best suited for smaller models with a very smooth surface finish. Able to produce very intricate details and features. Colours are limited.
Material jetting	The optimal solution for high detail, multi-colour, multi-material prints. Can also produce transparent parts. Surface finish is very smooth and models can be larger in size than FDM or SLA. More expensive than other AM technologies.
SLS	SLS can produce parts with very complex geometries and good strength. Parts are typically white with a matte-like grainy surface finish. Excellent for replicating bone.
FDM	FDM is ideal for geometrically basic surgical models that do not require a high level of detail or include intricate features. A large range of colours are available. Print layer lines will be visible.

Thermal Inkjet Printing (TIJ)

Inkjet printing is a “noncontact” technique that uses thermal, electromagnetic, or piezoelectric technology to deposit tiny droplets of “ink” (actual ink or other materials) onto a substrate according to digital instructions. In inkjet printing, droplet deposition is usually done by using heat or mechanical compression to eject the ink drops. In TIJ printers, heating the printhead creates small air bubbles that collapse, creating pressure pulses that eject ink drops from nozzles in volumes as small as 10 to 150 picoliters. Droplet size can be varied by adjusting the applied temperature gradient, pulse frequency, and ink viscosity.

TIJ printers are particularly promising for use in tissue engineering and regenerative medicine. Because of their digital precision, control, versatility, and benign effect on mammalian cells, this technology is already being applied to print simple 2D and 3D tissues and organs (also known as bioprinting). TIJ printers may also prove ideal for other sophisticated uses, such as drug delivery and gene transfection during tissue construction (66).