Rapid review of osseointegration/ direct skeletal fixation

A report for NHS England

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Bazian Ltd
20 Cabot Square, London E14 4QW
Phone: 020 7576 8156
Contact email: rosie.martin@bazian.com

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1. Executive summary

This report is an independent evaluation of the evidence base for the effectiveness and safety of lower limb osseointegrated prosthesis/direct skeletal fixation for the Armed Forces Direct Commissioning team within NHS England. Conventional socket prostheses rely on suction or strapping of the prosthesis to the stump which can cause a variety of problems and is often not possible at all. The term osseointegrated prosthesis includes all techniques that aim to avoid these problems by directly fixing the prosthesis to the bone. It involves insertion of a titanium rod into the residual bone of an amputee. An abutment is then attached to the rod and this permanently protrudes through the skin. The lower leg prosthesis can then be attached to this abutment. Variations of this procedure have been performed since 1990 mainly in national centres in Sweden, Germany and Australia but it has only been available as part of trials in the UK thus far. In this document, osseointegrated prosthesis is the generic term for these procedures, with the specific techniques referred to where applicable.

A search of biomedical and specialist databases for any human study published since 2000 on adult osseointegrated prosthesis found 23 observational studies of a total of 303 people who have undergone the procedure on 1 or both lower limbs. No randomised controlled trials were identified, so there is no high quality evidence on which to base recommendations. The main limitation of these case series is that with no matched control group we cannot be sure what the outcomes would have been if people had been given different types of osseointegrated prostheses or if they had not undergone the procedure.

Surgical techniques, devices and rehabilitation regimes have changed over the years but there are 3 main osseointegrated prosthesis techniques currently available called OPRA, Endo-Exo Femur Prosthesis and OPL for which the following results have been published:

- **OPRA**: 100 cases from a single centre in Sweden and 11 cases from a single centre in the UK. Good efficacy and safety profile with longest reported implant survival of 10 years in 3 cases. The main differences to the other procedures is the second operation to attach the abutment occurring after 6 months and then a slow rehabilitation schedule of 6 to 12 months with no weight bearing for the first 2 weeks after the second surgery.
- **Endo-Exo Femur Prosthesis:** (now termed IPL), 69 cases from a German centre and 22 cases from a centre in The Netherlands. Similar safety profile to OPRA with longest implant survival of 12 years, but limited data reported on efficacy. Second surgery performed after 6 weeks and then a faster rehabilitation regime with full weight bearing over a matter of days after the second surgery.
- **OPL:** (now termed OGAP-OPL), 101 cases from a single centre in Australia. Two conference abstracts report good efficacy and safety but with limited details and no long-term outcomes. The second operation is usually performed after 6 weeks but in some cases there is just a single operation fitting the rod and abutment at the same time. Rehabilitation with weight bearing is immediate and rapid.

Overall across these case series, quality of life assessed using standard questionnaires after 1 or 2 years showed substantial improvement though it stayed the same for a small proportion and worsened for a few cases. Mobility increased with the majority of people using the osseointegrated prosthesis on a daily basis. For each technique, between 5 and 7 people have had bilateral implants but further details are lacking.

Superficial infections were common and usually adequately treated with oral or intravenous antibiotics, though a large number of early cases required revision surgery. Newer surgical techniques and changes in the titanium rod appeared to reduce the number of infections. Deep infections were much less common, affecting between 1% and 8% of cases, with most requiring implant removal. The overall removal rate was 8% to 20%, but reimplantation was successful in half of these cases. No study reported on the outcomes for people for whom osseointegration was unsuccessful so it is not known if their situation was worse than before or not. There was no available data on deaths associated with osseointegration.

Implant structure failure was rare and bone fracture rate around the implant also appears to be very low at between 0% and 7% over up to 9 years. Pain remained severe 2 years after the first operation in 2% of cases and was intermittent during rehabilitation in 10% of cases, according to 1 case series. Implant stability was good up to 5 years with no bone resorption though there were some bone structural changes such as cortical thinning.

There was little available evidence on which to base the cost-effectiveness of the procedure. Only 1 small cost-effectiveness study was identified which looked at the costs of a specialist prosthetic workshop in Sweden. There are lifelong cost and support issues to consider, such as the number of revisions that may be required, whether new models of implants, abutments and prostheses remain compatible and the outcomes for people in whom the procedure is unsuccessful.

Most centres considered people to be eligible for the procedure if they had significant difficulties with the conventional socket prosthesis and were motivated and considered able to cope with the demands of the rehabilitation regime and lifelong care of the skin surrounding the protruding abutment (stoma). Common exclusion criteria across the centres were:

- Diabetes or vascular disease
- Chemotherapy or other immunosuppression
- Skeletal immaturity
- Poor bone quality (due to radiotherapy, osteoporosis, metabolic bone disease or renal insufficiency)
- Severe cognitive or psychiatric disorders

There are 4 registered trials ongoing or awaiting publication, including the ITAP trial of 20 adults from the UK which finished in December 2015. Outcomes of the OPRA Swedish case series of 51 people were last reported on in 2014, but data collection is planned to continue until 2027. The other 2 trials are about the types of bacteria on the stoma and use of the drug Denusomab to improve bone mineral density.

In summary, low quality evidence indicates that osseointegrated prosthesis improves quality of life for the majority of recipients and appears to be a safe procedure with only small numbers affected by the most important potential complication of deep infection. With a lack of high quality evidence and only limited long-term outcomes, osseointegration could be suitable for the NHS England Commissioning through Evaluation scheme (CtE) but there is insufficient evidence to recommend one technique over another. This is due in part to a lack of efficacy results for Endo-Exo Femur Prosthesis, little safety or efficacy data for OPL and none for ITAP. There are also no studies directly comparing the techniques. Commissioning of this procedure should include clinical governance, audit and standard assessments of long-term outcomes such as the Q-TFA and include all participants with no drop-outs or selective reporting so that this can better inform future decision-making.

2. Introduction

The Armed Forces Direct Commissioning team within NHS England requires an independent evaluation of the evidence base for osseointegration/direct skeletal fixation. More specifically, NHS England requires:

- An independent evaluation of the evidence for and against this procedure
- A recommendation as to which if any commissioning route to follow
- An estimate of the likely costs of a commissioning decision
- A recommendation of the types of patients who are most likely to benefit

This procedure involves the insertion of a titanium rod into the remaining bone of the amputated limb or digit. The rod penetrates through the skin and attaches to a prosthesis. The procedure has been used for people who have difficulties using the conventional socket approach whereby the limb is attached to the prosthesis through suction or strapping. Obtaining and maintaining a good fit between the socket and stump is challenging and a poor fit can lead to pressure sores, skin irritation, ulcers, fistula formation and pain[1]. Directly fixing the prosthesis to the bone through osseointegration aims to be a more comfortable and secure way of attaching the prosthesis and has been reported to improve control, stability and increase walking ability. Other activities that are possible with an osseointegrated prosthesis include cycling and swimming (if exposure to infection can be avoided or minimised) but running is not recommended due to the extreme forces involved.

This report focuses on the efficacy and safety of the procedure specifically for transfemoral (above the knee) osseointegration due to increasing demand, particularly among the armed forces community. In this document, osseointegrated prosthesis is the generic term for these procedures, with the specific techniques referred to where applicable.

3. Abbreviations

IPG	Interventional Procedure Guidance
ILP	Integral-Leg-Prosthesis
ITAP	Intraosseous transcutaneous amputation prosthesis
NICE	National Institute for Health and Care Excellence
NR	Not reported
OGAP-OPL	Osseointegration Group of Australia Osseointegration Prosthetic Limb
OPL	Osseointegration Prosthetic Limb
OPRA	Osseointegrated Prostheses for the Rehabilitation of Amputees
Q-TFA	Questionnaire for Persons with a Transfemoral Amputation
SF-36	Short Form Health Survey 36
TUG	Timed up and go test
6 MWT	6 minute walk test

4. Search

A systematic literature search was performed of biomedical databases, speciality databases, grey literature, citation searching and scanning reference lists. The searches included any study type with no restrictions or methodological filters as we aimed to identify all human studies including on-going trials and conference abstracts from 2000 to January 2016.

After deduplication of search results, 749 records remained. After an initial sift at title and abstract level, 86 records remained for the second sift, 57 were rejected and 29 studies were analysed at full text. Of these, 24 are included in this review. Further details of the scope are provided in Appendix A, the search strategy in Appendix B and excluded studies at full text in Table 5, Appendix C.

5. Existing national policies and guidance

The National Institute for Health and Care Excellence (NICE) provided Interventional Procedure Guidance (IPG) on 'Direct skeletal fixation of limb or digit prostheses using intraosseous transcutaneous implants' in 2008[2]. They recommended that the procedure is only performed if there are special arrangements for clinical governance, consent and audit or research. This was due to a lack of evidence at the time on the safety and effectiveness of the procedure and in particular the long-term outcomes.

6. Epidemiology

There are around 45,000 amputee and limb deficient people in England[3]. Each year about 4,000 major lower limb amputations, 200 upper limb amputations and 150 congenital upper and lower limb amputations are referred to about 30 specialist centres[3]. The vast majority of lower limb amputations are conducted in the elderly population due to vascular disease and diabetes which is estimated to be around 90% of cases according to an MoD report from 2008[4]. In the UK from 2011 to 2012 there were 171 transfemoral amputations due to trauma (13 bilateral), 78 due to tumour and 174 from infection, the 3 main reasons for amputation in most recipients of osseointegration thus far[5]. Unsuccessful fitting of a transfemoral socket prosthesis is estimated to occur in 30% and 60% of cases[4], so between 127 and 254 people each year may be suitable candidates for an osseointegrated prosthesis, though this will also depend on other inclusion and exclusion criteria.

With regards to the armed forces, a recent study found that as a result of the Afghanistan conflict between 2003 and 2014 there were 416 amputations in 265 individuals, with above the knee amputations affecting 153 people[6]. They calculated that the cost of lifetime care for veterans with amputations from the Afghanistan conflict alone is £288 million. While these costs do not solely include prostheses, it does indicate the magnitude of the issue.

7. The intervention

Osseointegration originated in dental implants but has also been used for people with amputations since the early 1990s. The basic concept is that a titanium rod is inserted into the bone of the residual limb, such as the femur, and the skin is closed. Bone cells then gradually attach to the titanium, holding it in place. After either 6 weeks or 6 months depending on the centre's protocol, a second operation is performed to attach the rod to a metal abutment (connector) which protrudes through the skin. This abutment can be attached to the external prosthetic limb and there is a safety release feature in case of falls.

The opening of the skin and soft tissues around the abutment is called the stoma and depending on the technique used, the skin either seals onto the abutment or slides along it during walking. It is common for there to be secretions from the stoma and this may continue beyond the initial healing period. Care needs to be taken of the stoma for life to keep it clean so as to avoid infection. This includes prompt eradication of ingrowing hairs such as through laser hair removal.

The 2-stage operation was conceived so that the osseointegration of the bone and titanium rod would take place in a "closed" environment, reducing the risk of deep infection in the bone. However, the Osseointegration Group of Australia Osseointegration Prosthetic Limb (OGAP-OPL) centre and Intraosseous transcutaneous amputation prosthesis (ITAP) in the UK now perform the procedures in 1 operation in appropriate candidates.

Over the years, other changes in technique have included debulking the soft tissue, refining any residual burn or scar tissue and removing subcutaneous fat from around the abutment.

Rehabilitation protocols have also changed and still differ across the centres that offer osseointegration. The Osseointegrated Prostheses for the Rehabilitation of Amputees (OPRA) system that originated in Sweden favours a slow rehabilitation protocol after the second operation over 24 weeks or 48 weeks with no weight bearing for the first 2 to 4 weeks and utilising a short prosthesis before graduating to full height. Whereas the Integral-Leg-Prosthesis (ILP) system from Germany (previously called Endo-Exo Femur Prosthesis) and the OGAP-OPL system prefer immediate partial weight bearing with full weight bearing without crutches after 4 to 6 weeks. Further details of the various centres offering osseointegration are provided in Table 1 including the number of cases that have been reported in the literature for these centres.

Table 1: Osseointegration techniques currently available

Procedure	Company	Cases reported and dates	Intervention details	Countries offering technique
Osseointegrated Prostheses for the Rehabilitation of Amputees (**OPRA**)	Integrum, Molndal, Sweden[7]	100 cases 1990-2008	**Procedure[8]:** 2nd operation after 6 months, also involves splitting muscles at the end of the implant and suturing them to the bone, leaving a portion of 5mm bare bone covered by skin that has had the subcutaneous fat removed. **Rehabilitation[9]:** Normal speed 6 months (or half speed 12 months). Immobilisation for 1-2 weeks. Training with short prosthesis starting with 20kg at 4-6 weeks. Training with full prosthesis 11-13 weeks. Discuss when can walk without a walking aid at 24 weeks.	Sweden, Australia, Belgium, Denmark, France, The Netherlands, Portugal, Spain, Australia, USA and Chile
Endo-Exo Femur Prosthesis, now termed Integral-Leg-Prosthesis (**ILP**)	Sana Clinics Lübeck, Germany[10]	69 cases 1999-2013	**Procedure:** 2nd operation after 6 weeks. **Rehabilitation:** Partial weight-bearing 5-10kg with crutches and vertical posture immediately after second surgery. Full weight-bearing without crutches after 4 to 6 weeks.	Germany, The Netherlands and Australia
Intraosseous transcutaneous amputation prosthesis (**ITAP**)	Stanmore Implants Ltd, UK[11]	None yet reported	**Procedure:** 1 stage operation. **Rehabilitation:** No details provided.	Only available as part of a pre-CE mark clinical study in the UK.
Osseointegration Prosthetic Limb (**OPL**) now termed Osseointegration Group of Australia Osseointegration Prosthetic Limb (**OGAP-OPL**)	Osseointegration Group of Australia[12]	101 cases 2011-2015	**Procedure:** 1 single operation or 2nd operation after 6 to 8 weeks. Redundant skin and any bone spurs are removed, muscle groups are rearranged and soft tissue fat is removed. **Rehabilitation:** Partial weight-bearing and fitting of prosthesis days after surgery.	Australia
OPRA	A Step Ahead Prosthetics, USA[13]	None yet reported	No details provided.	USA, Israel

8. Findings

A search for all human studies for lower limb osseointegration identified 1 systematic review[1] and 23 primary studies, several of which were reported as conference abstracts only. The primary studies included 9 prospective case series, 9 retrospective case series, 4 case series with nominal control groups such as socket users or people without limb loss and 1 retrospective cost analysis. There were no randomised controlled trials. Thus all studies were observational in nature, with many being retrospective which limits the strength of the body of evidence. The main limitation of these case series is that with no matched control group we cannot be sure what the outcomes would have been if people had been given different types of osseointegration prostheses or if they had not undergone the procedure.

The studies reported on 303 cases from single centres in 5 countries, shown in Table 2. Several of these studies reported on interim results for sub-sets of the same cases at different time points or according to specific outcomes, so the main and most recent results are reported here to avoid repetition. Comparisons and reporting is further complicated by evolving techniques, equipment and rehabilitation regimes over the years. Some studies had short follow-up periods of 1 to 2 years whilst others had longer follow-up but with selective reporting and they often do not report how participants were recruited so there is an element of selection bias.

No evidence was found on employment and return to work outcomes - other than 3 out of 11 cases from the UK who were in full-time employment following the procedure compared to 1 beforehand.

Only 1 cost analysis study was identified which provided limited information regarding socket prosthetic costs compared to osseointegration prosthetic costs at a single specialist prosthesis workshop in Sweden.

Demographics

There was no notable difference in the demographics of recipients of each of the different types of osseointegrated prostheses. The average age at time of amputation was around 33 in each centre, with a wide age range of 1 to 76. The average age at implantation was also similar in each centre at around 45 years, with a range of 17 to 76 years. There were more men than women with OPRA and Endo-Exo Femur Prosthesis but sex was not reported for OPL. Further details are provided in Table 2.

The majority of subjects had amputations due to trauma or tumour, with a handful due to infection or congenital conditions. All had significant difficulties with the conventional socket prosthesis. The studies did not split the effectiveness or safety outcomes according to the reason for amputation. Between 1 and 7 cases per centre received bilateral implants except in the UK. All 6 people with OPRA from the Swedish centre were using them at follow up but no further details were provided in any study about efficacy or safety of bilateral implants.

Most studies excluded participants for the following reasons:

- Diabetes or vascular disease
- Chemotherapy or other immunosuppression
- Skeletal immaturity
- Poor bone quality (due to radiotherapy, osteoporosis, metabolic bone disease or renal insufficiency)
- Severe cognitive or psychiatric disorders

Other reasons for exclusion at some centres included:

- Body mass greater than 100Kg[14]
- Age less than 20 or more than 70 years[8, 9, 14]
- Skin disease affecting amputation[8]
- Femur less than 8cm[15]

Technique and rehabilitation modifications

The 2 largest case series with the most comprehensive details split their data according to changes in technique or rehabilitation. Out of the 100 cases of OPRA from Sweden during the period 1990 to 2008, 51 of them were reported in a separate study as the centre had instituted a standard rehabilitation protocol for them in 1999, of either 12 months or 18 months depending on individual circumstances. The German centre split their results into 2 groups – 30 cases of the original Endo-Exo Femur Prosthesis designs from 1999 to 2008 and 30 cases with a modified, smaller design with a different implant coating and an altered surgical technique from 2009 to 2013. All available evidence from these studies will be reported on in the effectiveness and safety sections where relevant but further details of all studies can be found in Table 6, Appendix D.

Table 2: Studies identified in search

Country	Study periods	Total number of cases	Intervention	Demographics	Studies
Sweden	1990-2008	100 6 bilateral implants	OPRA	61 males, 39 females Average age at amputation: 32±13.9 years (range 10 to 63 years) Average age at implantation: NR Years since amputation when implanted 11.5±11 years (range 0 to 44 years) Reason for amputation: • Trauma (N=67) • Tumour (N=21) • Infection (N=7) • Vascular including embolus (N=3) • Diabetes (N=2) 74 people used a socket prosthesis on at least 1 day a week	Branemark 2014[16] Hagberg 2014[17], 2009[9], 2008[18], 2005[19] Haggstrom 2013[20], 2013[21] Nebergall 2012[22] Tranberg 2011[23] Frossard 2010[24] Tillander 2010[25]
UK - Roehampton	1997-2003	11 No bilateral implants	OPRA	Sex: NR Average age at amputation: NR Average age at implantation: NR Unable to use socket technique	Sullivan 2003[14] Hagberg 2005[19]
Germany	1999-2013	69 4 bilateral implants	Endo-Exo Femur Prosthesis, now called ILP	56 males, 13 females Average age at amputation: 34.5±14.2 years (range 14 to 76 years) Average age at implantation: 45.4±12.3 years (range 17 to 76 years) Reason for amputation: • Trauma from RTAs (N=51) • Tumour (N=7) • Infected total knee arthroscopy (N=3)	Juhnke 2015[26] Aschoff 2014[27], 2014[28], 2012[29], 2011[30], 2010[31], 2009[32]

				• 4th degree burn (N=1) • Other (N=7) Socket information: NR	
The Netherlands	2009-2011	22 1 bilateral implants	Endo-Exo Femur Prosthesis	18 males, 4 females Average age at implantation 46.5 (range 23 to 67 years) Average time since amputation 16.4 years (range 2 to 45 years) Reason for amputation: • Trauma N=20 • Tumour N=2 Significant socket related problems affecting quality of life	Van de Meent 2013[15] Al Muderis 2015[33]
Australia	2011-2015	101 7 bilateral implants	OPL (Osseointegrated Prosthetic Limb), now called OGAP-OPL	Sex: NR Average age at amputation: 33 (range 3 to 76 years) Average age at implantation 44.3 (range 17 to 76 years) Reason for amputation: • Trauma (N=77) • Infection (N=12) • Tumour (N=10) 30% wheelchair-bound	Khemka 2015[34], 2015[35] Al Muderis 2015[33]

9. Evidence of effectiveness

Efficacy outcomes have broadly been split into quality of life assessments, mobility, implant longevity, hip range of motion and vibrotactile sensation though there is some overlap across these sections. Standard outcome measures were not used consistently across the identified studies which makes synthesis of the results challenging.

Overall there was a significant improvement in quality of life for the majority of people across the studies when assessed using standard questionnaires after 1 or 2 years, though it stayed the same for a small proportion and worsened for a few cases. Mobility increased according to several case series with a substantial number of people using the osseointegrated prosthesis on a daily basis. The longest reported time that implants were still intact was 10 years for OPRA and 12 years for Endo-Exo Femur Prostheses. A small case series suggested that OPRA improved gait when compared to that of a group of socket users and that it was normalising towards that of people without limb loss but this study was of low quality and subject to selection bias.

No evidence was found of the effectiveness of osseointegration implants for:

- Confidence
- Return to work/vocational outcomes
- Bone mineral density

Quality of Life

Mean improvements in prosthetic use, mobility and reduced problems were found according to the Questionnaire for Persons with a Transfemoral Amputation (Q-TFA) in the first 1 or 2 years after implantation for 51 cases of OPRA from Sweden and 16 people with OPL from Australia. Results of the Short Form Health Survey 36 (SF-36) also showed mean improvements in physical function and physical role functioning for the 51 OPRA cases with no change in other domains. The overall situation improved for the majority of these cases plus 22 people with Endo-Exo Femur Prosthesis from The Netherlands and 9 cases from the UK. Of note, the situation was unchanged for 24% of the OPRA case series and got worse for 7%. A small study found that OPRA caused little sitting discomfort compared to that experienced by a group of socket prosthesis users but it is unclear how the subjects were recruited which makes it subject to selection bias.

Q-TFA:

The Q-TFA is a self-reported questionnaire which is used to assess function and quality of life. Each domain is scored from 0 to 100 with higher scores indicating better quality of life except for the problem score. Three studies reported Q-TFA outcomes as follows:

- Mean prosthetic use score (0 = no use, 100 = more than 15 hours per day for 7 days):
  - Increased from 52 to 70, $p<0.001$ in 51 people with OPRA over 2 years follow-up[8].
  - Increased from 63 to 91 for 16 people between 6.5 months and 24 months after OPL Stage 1 surgery in Australia (56% reported an improvement)[34].

- Mean prosthetic mobility score:
  - Increased from 52 to 70, $p<0.001$ in 51 people with OPRA over 2 years follow-up[8].
  - Increased from 64 to 82 for 16 people between 6.5 months and 24 months after OPL Stage 1 surgery in Australia (75% reported an improvement)[34].

- Mean problem score (0 = no problems):
  - Reduced from 44 to 17, p<0.001 in 51 people with OPRA over 2 years follow-up[8].
  - Reduced from 40 to 8 for 16 people between 6.5 months and 24 months after OPL Stage 1 surgery in Australia (94% reported an improvement)[34].

- Mean global score:
  - Increased from 38 to 77, p<0.001 in 51 people with OPRA over 2 years follow-up[8].
  - Increased from 47 to 79 for 16 people between 6.5 months and 24 months after OPL Stage 1 surgery in Australia (69% reported an improvement)[34].
  - Increased from 39 to 63 for 22 Endo-Exo Femur Prosthesis recipients in the Netherlands after 1 year follow-up[15].

SF-36

The SF-36 is a general health related questionnaire which is also scored on a scale of 0 to 100 with higher scores indicating a better quality of life. This assessment was only reported in the OPRA 2 year follow-up of 51 people, with the following results[8]:

- Physical function improved from 35 to 58, p<0.001.
- Physical functioning role improved from 41 to 63, p<0.001.
- Other parameters did not change significantly such as vitality, bodily pain, general health perceptions, emotional and social role functioning.

Sitting discomfort

One non-randomised case series compared reports of sitting discomfort from 20 people with OPRA for at least 2 years and able to walk 100m or more, and 43 socket prosthesis users in Sweden[19]. The results are as follows, but should be interpreted with caution as there was no attempt to match the control group with the OPRA group and so the study has major limitations due to selection bias:

- 5% of the osseointegrated group reported sitting discomfort compared to 44% of the socket user group.

Overall situation

The overall situation improved for most people given osseointegration prostheses according to 2 case series as follows:

- According to 1 question on the Q-TFA, the overall situation improved for 31/45 (69%) people, stayed the same for 11/45 (24%) and got worse for 3 (7%) people in the 2 years following OPRA[8].
- The UK study of 11 cases of OPRA did not use any standard quality of life assessments over the 5.5 years of follow-up[14]. However, they reported that 9 cases had improved quality of life such as better proprioception, ability to walk further and do more, no longer feeling disabled and ability to participate with full daily living and activities such as cycling. Negative aspects included longer rehabilitation than expected and a high number of visits for rehabilitation.

Mobility

The majority of people used their osseointegrated prosthesis on a daily basis according to 4 case series over a follow-up period of 1 to 17.5 years. It is not clear if a single implant lasted 17.5 years or if they had been replaced. Gait analysis was assessed in 12 people with an osseointegrated implant and showed marginally better cadence and duration of gait cycle compared to socket prosthesis users from the literature, though methodological issues limit the reliability of these results. Other tests

performed on 22 people with an Endo-Exo Femur Prosthesis gave encouraging results in 6 minute walk test, timed up and go test and oxygen consumption.

Prosthetic use:

Three case series reported directly on prosthetic use as follows:

- 40/45 had daily prosthetic use (1 no use due to pain, 4 less than daily use) compared with 29/51 before implantation in the 2 year follow-up of the OPRA case series from Sweden[8]. In the larger case series of 100 people with OPRA performed in the Swedish centre between 1990 and 2008, 68 people with 74 prostheses were still using them by 2008[9]. There are no details as to whether any had lasted the full 17.5 years.
- Mean use increased from 56 to 101 hours/week for 22 people with Endo-Exo Femur Prosthesis in the Netherlands after 1 year follow-up[15].
- Daily use was reported in 9/11 cases from the UK during a maximum follow-up of 5.5 years[14].

Gait analysis

The gait of 12 participants from Sweden and Australia with unilateral osseointegrated implant for at least 1 year and able to walk unaided 200m or more was compared to data sets from the literature of 142 people with transfemoral amputation fitted with a socket, and 258 participants without limb loss[24]. The results should be interpreted with caution due to selection bias and non-standardised assessments for each group which may not have been conducted under the same conditions, but were reported as follows:

- Cadence was 46 strides/minute, which was 2% faster than for those using a socket prosthesis and 11% slower than people without limb loss.
- Gait cycle was 1.29 seconds, 3% shorter than for those using a socket prosthesis and 9% longer than people without limb loss.
- Swing phase of the gait cycle was slightly longer than for people with a socket prosthesis or those without limb loss.

Other tests:

The case series of 22 people with Endo-Exo Femur Prosthesis in the Netherlands showed improved performance on the following 3 tests after 1 year[15]:

- 6 minute walk test (6 MWT) increased on average from 321m to 423m.
- Timed up and go test (TUG) improved from 15.1 seconds to 8.1 seconds.
- Oxygen consumption reduced from 1330mL/min to 1093mL/min.

Implant longevity

Due to the short length of follow up, changes in technique, improved design and small numbers of cases, it is not clear how long osseointegrated prostheses are likely to last. The longest time an Exo-Endo Femur Prosthesis is reported to have lasted is 12 years[36]. For OPRA, there have been 3 reported cases lasting 10 years[22].

Hip range of motion

Hip range of motion was assessed in 2 small case series with non-matched “control” groups, both limited by selection bias. They found that OPRA improved hip range of motion and pelvic tilt:

- Hip range of motion of 20 people from the UK and Sweden with OPRA for at least 2 years and able to walk for at least 100m was compared to 43 socket prosthesis users in Sweden[19]:

  - There was no hip range of motion restriction for the OPRA group (none had less than 90° hip flexion) compared to it being reduced in all directions with a socket prosthesis (37% had less than 90° hip flexion).
- Hip extension and anterior pelvic tilt of 19 people was recorded before and 2 years after OPRA and compared to 57 people without limb loss in Sweden[23]:
  - Hip extension increased by 7.3° from -2.6°(range -13.4° to 10.7°) to -9.9°(range -29.4° to 5°), p=0.007, reportedly improving towards the result for people without limb loss, though data was not provided.
  - Anterior pelvic tilt reduced by 4° from 21.7° (range 11.9° to 34.8°) to 17.7° (range 5.5° to 25.7°), p=0.016, also reportedly improving towards the result for people without limb loss, but data was not provided.

Vibrotactile sensation

Vibrotactile sensation was assessed in 1 small case series of 17 people before and 2 years after OPRA in Sweden and compared to 17 people with socket prostheses[20].

- Detection threshold improved by 10 Decibels (Db) for high frequencies of 125Hz and 250Hz (from 110Db to 100Db for 125Hz and from 122Db to 111Db for 250Hz).
- There was no change for lower frequencies of 8Hz, 16Hz, 32Hz and 64Hz.
- These results were better than for the people who used socket prostheses.

Other outcomes

- The case series of 101 people with lower leg OPL performed in Australia reported significant improvement for Q-TFA, SF-36, K-scores (functional ability), TUG and 6 MWT. Energy expenditure increased 4-fold. No further details were provided in the conference abstract, but this case series included people with below knee OPL[35].
- No efficacy outcomes were reported for the case series of Endo-Exo Femur Prostheses performed in Germany[36].

10. Safety

Safety outcomes were not consistently reported across the studies and were often only recorded in the first 2 years, which hampers the ability to draw firm conclusions or make any comparisons between the techniques. Though each of the following safety issues is reported in percentages, they are based on small numbers and often over short follow-up periods.

Superficial infections were common and usually adequately treated with oral or intravenous antibiotics, though a large number of Endo-Exo Femur Prosthesis cases required revision surgery. Newer techniques and changes in the size, shape and coating of the titanium rod appeared to reduce the number of infections. Deep infections were much less common, affecting between 1% and 8% of cases, with most requiring implant removal. Other causes of implant removal were failure to osseointegrate and aseptic loosening. The overall removal rate was 8% to 20%, but reimplantation was successful in half of these cases. No study reported on the outcomes of people for whom osseointegration was unsuccessful so it is not known if their situation was worse than before or not.

Implant structure failure was only reported in 1 case across all studies and abutment fracture or bending in 9 cases. Bone fracture rate around the implant also appears to be very low at between 0% and 7% over up to 9 years. Pain remained severe 2 years after the first operation in 2% of cases and

was intermittent during rehabilitation in 10% of cases, but this was based on 1 case series. Implant stability was good up to 5 years and there was no bone resorption though there were some bone structural changes such as cortical thinning. There was no available data on deaths associated with osseointegration.

Superficial infection

Across 5 case series of implants performed in Europe and Australia, superficial soft tissue infections were commonly reported, occurring in between 32% to 96% of cases. Most were treated successfully with oral antibiotics though many required hospital admission and surgery. Three of these studies were conducted over a 2 year period so do not provide data on more long-term infection rates. The lengthier case series from the German centre over 9 years only reported infection rates requiring surgical intervention so it is not clear how many cases of less severity occurred which may have responded to antibiotics. In this case series the rates of infection requiring surgery were higher in the early years at 77%, but dramatically reduced to zero following changes in technique and implant device. While this is encouraging, the shorter follow-up period for these later cases may have affected the results.

The results of each national centre are as follows:

- Revision surgery for infection occurred in 77% of cases (23/30) fitted with early versions of Endo-Exo Femur Prosthesis in Germany between 1999 and 2008, but in none of the cases (0/39) fitted using the newer design and technique between 2009 and 2013[36]. This study did not report on the number of soft tissue infections treated with oral or intravenous antibiotics, nor did any previous interim publications[26-32, 36].
- There was a 55% infection rate with OPRA implants over a 2 year follow-up period in Sweden up to 2007[16]. This occurred 41 times in 28 out of 51 cases. All instances were treated with antibiotics, 4 of them in hospital.
- There was a 32% infection rate) over a 2 year follow-up period in operations performed in Australia (12/22) after 2011 when OPL was introduced. Seven people were treated with oral antibiotics and 5 required surgical intervention[33]. The same surgeon performed OPL on 101 lower limb amputees according to a conference abstract, but infection rates were not reported[35].
- Soft tissue infection occurred in 96% of Endo-Exo Femur Prosthesis cases performed in The Netherlands (23/24) in the first 2 years after implantation from 2009 to 2011. Fifteen were treated with antibiotics and 8 required surgical intervention[33].
- The UK case series of 11 people with OPRA from 1997 to 2003 did not provide details on superficial infection rate[14].

Deep infection

Osteomyelitis occurred in 1% to 8% of cases. A higher percentage of 18% was found in the UK study but this was due to the small study size of just 11 people. The deep infections mainly required surgical interventions and most caused implant failure.

The results of the national centre are as follows:

- The Endo-Exo Femur Prosthesis cases in the German centre between 1999 and 2008 had a 3% rate of intramedullary infection (1/30), with no cases from the newer design and technique during 2009 and 2013 (0/39), giving an overall rate of 1%[36]. The infection led to removal of the implant. Skeletal immaturity was believed to have contributed to poor osseointegration, leading to the infection. A further report on this case series including an additional 5 people

with Endo-Exo Femur Prosthesis prostheses by the same author reported an incidence of intramedullary infection of 5% (4/74)[26].

- A deep infection rate of 8% occurred in OPRA cases from the Swedish centre (4/51) over a 2 year follow-up period[8]. One led to loosening and removal, 1 was treated with oral antibiotics and 2 had positive cultures at surgery with no signs of infection and they were treated with oral antibiotics for 6 months.
- Osteomyelitis causing implant failure occurred in 4% of OPL cases (1/22) performed in Australia over a 2 year follow-up period[33].
- Osteitis (inflammation of the bone) requiring surgical intervention occurred in 4% of Endo-Exo Femur Prosthesis cases (1/24) in The Netherlands centre over a 2 year follow-up period from 2009 to 2011[33].
- Deep infections affected 18% of cases of OPRA from the UK centre (2/11) during the first year and required implant removal[14].

Removal

Overall, 8% to 20% of implants were removed. Causes included failure to osseointegrate, infection and aseptic loosening. Reimplantation was successful in half of these cases. No information was provided on outcomes such as mobility or complications in people who had had an unsuccessful implant.

The results for each national centre are as follows:

- 6% of Endo-Exo Femur Prosthesis implants were removed at the German centre. All occurred in the group of people from 1999 to 2008 (4/30) due to a failure to osseointegrate, though half were reimplanted. No implants were removed in the group from 2009 to 2013 (0/39)[36].
- 20% of OPRA implants were removed from the large Swedish case series (20/100) between 1990 and 2008 but no details were provided on the cause[9]. Of these, 13 cases were reimplanted, 9 of which were successful. When looking at the more recent sub-set of this case series between 1999 and 2007, 8% of implants (4/51) were removed[8]. Three of these were due to aseptic loosening causing pain on weight-bearing and 1 was due to infection.
- 18% of OPRA implants (2/11) were removed within the first year due to infection in the UK case series from 1997 to 2003[14].
- The number of implants that were removed was not reported for the case series of OPL from Australia[33-35] or Endo-Exo Femur Prosthesis from The Netherlands[15, 33].

Implant or abutment structure failure

Failure of the structure of the implant was rare, occurring in just 1 case from the German case series. Fracture or bending of the abutment was slightly more frequent, especially due to falls, occurring in 9 people with OPRA from Sweden and the UK.

The results for each national centre are as follows:

- In the German Endo-Exo Femur Prosthesis case series, there was 1% implant structure failure. The case occurred at 7 years from the early group (1/30) implanted between 1999 and 2008. There were none in the more recent group from 2009 to 2013 (0/39)[36].
- 9 fractures or bending of the abutment or screw occurred (4/51) – 6 in the same person - in OPRA cases from Sweden between 1999 and 2007[8].
- 45% of OPRA abutments were replaced due to mechanical deformation or fracture (5/11) in the UK following falls[14]. None of the implants were damaged.
- Implant or abutment structure failure was not reported for the case series of OPL from Australia[33-35] or Endo-Exo Femur Prosthesis from The Netherlands[15, 33].

Fracture

Overall there was a lack of data on the frequency of fractures around the implant. The Endo-Exo Femur Prosthesis case series from Germany had an overall fracture rate of 7%. There were fewer cases with the newer technique, but again the shorter length of follow up could have affected the results, especially when looking at such small sample sizes. No fractures were reported around the OPRA implant in the case series from the Swedish centre over the period from 1999 to 2007, though 3 people had hip fractures.

The results of each national centre are as follows:

- A 10% fracture rate was experienced in the group of people in Germany from 1999 to 2008 (3/30) over the first 6 months following osseointegration with Endo-Exo Femur Prosthesis and 5% in the group (2/39) from 2009 to 2013 which occurred after 31 and 34 months[36]. This gave an overall fracture rate of 7%.
- In the Swedish case series 6% (3/51) had fractures of the hip of the affected limb over the period from 1999 to 2007[8]. There was also 1 below the elbow fracture and 1 vertebral compression. The larger case series covering an additional 49 cases from 1990 to 1999 did not report on the incidence of fractures[9].
- Rate of fracture was not reported for the case series of OPL from Australia[33-35], Endo-Exo Femur Prosthesis from The Netherlands[15, 33] or OPRA from the UK[14].

Pain

Only the case series from Sweden reported on pain as an outcome.

- Almost constant pain was reported by 2% of people with OPRA (1/51) up to 2 years after the implantation[8]. Intermittent pain during the rehabilitation phase occurred in 10% of people (5/51). In the larger case series 2% had severe phantom limb pain (2/100) and 1% had contralateral limb pain (1/100)[9].
- Pain outcomes were not reported for the case series of Endo-Exo Femur Prosthesis from Germany[26-32, 36] or The Netherlands[15, 33] , OPL from Australia[33-35], or OPRA from the UK[14].

Long-term implant stability and bone structure

Long-term fixation and stability was assessed in the OPRA Swedish case series of 51 people, with around 50 cases assessed in the first 2 years but just 15 cases by year 5 which limits confidence in the results[22].

- At the 5 year assessment there appeared to have been very little movement of the implant within the bone. The implant had moved downward on average 0.02mm and rotated on average 0.42 degrees.
- Cancellization of the cortex (increased porosity) occurred in at least 1 out of 12 zones in over half of cases by the first year after implant. The number of cases affected increased by year 2 but decreased by year 5.
- Cortical thinning also occurred in some cases which was obvious from the first year of follow up.
- There was very rarely any bone resorption.

Death

There was no data available on deaths related to osseointegration. Any deaths in study participants were reported as follows:

- Overall there were 4 deaths in the OPRA Swedish case series of 100 people[9]. There were 3 deaths before the second operation was performed - 1 of these was described as unrelated to the implant procedure when reported in the subset study of 51 people[8, 9]. The causes of the other 3 deaths were not reported.
- Deaths were not reported for the case series from Germany[26-32, 36], Australia[33-35], The Netherlands[15, 33] or the UK[14].

11. Evidence of cost-effectiveness

One cost-effectiveness study was identified but it was of low methodological quality[21]. Costs of socket prostheses and the external components of osseointegrated prostheses were calculated retrospectively from a prosthetic workshop in Sweden between 1993 and 2008. The costs included salaries, new prostheses, services, repairs, adjustments and maintenance but did not include costs associated with initial surgery, clinic appointments or other health related costs.

The total cost per year was higher for socket prostheses users at €3,672±2,259 compared to €3,149±1,682 for those with osseointegrated prostheses, based on 2009 prices. People with socket prostheses also had more than double the number of visits to the workshop per year, with a mean number of 7.2±4.2 visits compared to 3.1±1.5 visits for people with osseointegrated prostheses. Of note, this was a specialised prosthetic clinic for people who had extra difficulties with their socket prosthesis so this may not be an entirely representative sample of socket prosthesis users in general.

The average cost to manufacture a new prosthesis in 2009 was more than double for the external components of the osseointegration prostheses at €9,370±6,441 compared to the components of a socket prosthesis at €4,890±1,758.

No evidence was found on value for money of osseointegration implants such as:

- Return on prosthetic investment
- Costs of stump management
- Reduced obesity, vascular disease and diabetes risk
- Speed of return to work/normal activities of daily living

12. Trials in progress

There are 4 registered trials that are ongoing or awaiting publication, 2 are open label/efficacy studies, 1 study will look at the bacterial composition around the stoma and 1 double blind randomised controlled trial will assess whether use of the drug Denusomab helps to improve bone mineral density.

Stanmore study

Direct Skeletal Fixation of Prosthetic Limbs Following Trans-Femoral Amputation - Study of an Intraosseous Transcutaneous Amputation Prosthesis (ITAPTM) NCT02491424

This UK study has finished and the results are awaited - no preliminary results are available.

Device:	Direct skeletal fixation of ITAP to lower limb amputees.
Locations:	United Kingdom, Royal Orthopaedic, Birmingham and Royal National Orthopaedic Hospital, Stanmore
Sponsor:	Stanmore Implants Ltd.
Enrolment:	20 adults with traumatic transfemoral amputation
Study design:	Open label safety/efficacy study
Study Start Date:	January 2007
Estimated Primary Completion Date:	December 2015
Estimated Study Completion Date:	February 2016

OPRA study

Osseointegrated Prostheses for the Rehabilitation of Amputees (OPRA) NCT01725711

This study has been running since 1999 when the standardised rehabilitation protocol was implemented. Interim results of this study have been reported throughout this report, and they intend to continue to report effectiveness and safety outcomes until 2027.

Device:	OPRA Implant System
Location:	Sweden, Sahlgrenska University Hospital, Gothenburg
Sponsor:	Integrum
Enrolment:	51 adults with transfemoral amputation not due to vascular disease
Study design:	Open label safety/efficacy study
Study Start Date:	May 1999
Estimated Study Completion Date:	May 2027

Microbiome trial

Microbiome and Innate Immunity with Percutaneous Osseointegrated Prostheses NCT02564432

This study is not yet open for participant recruitment. The aim is to record changes/evolution in bacterial ecology around the exit site (stoma) at intervals up to 1 year and changes in the individual microbiome of each patient will be compared against him/herself and against the other 10 patients.

Device:	A novel percutaneous osseointegrated prosthetic (POP)
Location:	Salt Lake City, Utah

Sponsor:	VA Office of Research and Development
Estimated Enrolment:	10 US veteran or active military personnel with transfemoral amputation
Study Start Date:	October 2015
Estimated Study Completion Date:	September 2018
Estimated Primary Completion Date:	September 2017 (Final data collection date for primary outcome measure)

Denusomab trial

Osseointegrated transdermal femoral amputation prostheses - Denusomab Trial EUCTR2012-003574-66-DK

Device:	Use of Denusomab to improve bone mineral density
Location:	Denmark
Sponsors:	Aarhus Universitet, Karen Elise Jensens Fond
Enrolment:	28 adults with transfemoral osseointegrated prostheses (14 aged 65 or over)
Study design:	Randomised placebo-controlled double blind trial
Study Start Date:	2013
Estimated Study Completion Date:	2016

13. Equity issues

The potential equity issues include age, body build, bilateral or unilateral amputations and mental health conditions.

Age

Older age was an exclusion criterion in 3 national centres, where the cut-off was 70 years. However a 76 year old was given an Endo-Exo Femur Prosthesis in the German centre which was performed the same year as the amputation. No further details are available about the success of the implant for this individual. The case series of OPL from the Australian centre also included at least 1 person aged 76 at the time of amputation and implantation, though again no further details on outcomes has been published. Restricting the procedure solely based on an upper age limit may be discriminatory and it could be more appropriate to look at overall fitness and likely ability to cope with the rehabilitation.

The younger age cut-off in each centre was either 20 years or described as “skeletal immaturity”. A case of Endo-Exo Femur Prosthesis from the German centre that failed to osseointegrate was deemed to be due to skeletal immaturity. Further details of this case are not available, but the youngest person to have had the procedure was 17 years old. Though this is only 1 case, it seems reasonable to continue the exclusion criterion of skeletal immaturity.

Body build

The size of the implant and thus the requirement for a certain width and length of residual femur may limit its use in people of smaller build and this may affect more women than men. Weight over 100Kg was an exclusion criteria in the UK case series[14] because of concerns about weight-bearing on

the implant and abutment. Overweight or obesity were not listed as exclusion criteria in any of the other case series. There are no available details about weight and outcomes.

Bilateral or unilateral amputations

Several case series included a small number of bilateral amputees, some of whom had 1 or both limbs fitted with an osseointegrated implant. The studies do not report any difference in outcomes for these people compared to those with unilateral limb loss, so there is no evidence to suggest that this should be a reason not to perform the procedure.

Mental health conditions

Any psychiatric conditions and low intelligence were listed as exclusion criteria in most case series due to concerns over the ability to cope with the rehabilitation regime and lifelong stoma care. However, it would seem more reasonable to look at this on a case by case basis according to level of severity, social support and the potential improvements in quality of life that osseointegration may bring.

As inability to use a socket prostheses can contribute to both obesity and certain mental health disorders such as depression, these may be conditions that need more careful consideration before exclusion.

14. Implications for commissioning

The NICE 2008[2] recommendation for osseointegration to be performed only if special arrangements are made was based on the lack of available evidence of effectiveness, safety and in particular long-term outcomes. At that time, there were only 2 non-randomised comparative studies and 3 case series which included osseointegration for 39 lower limb amputees. Though there is now published evidence for 303 people who have undergone transfemoral osseointegration, there are still no randomised controlled trials and there remains limited evidence of long-term outcomes.

It is difficult to draw firm conclusions regarding which type of osseointegration model or technique is to be recommended over any other. Most case series provided results of 1 lead surgeon and multidisciplinary team from a single centre so it is not possible to separate the effect of the expertise, technique or implant type. Results specifically for the UK are currently confined to those from Queen Mary's Hospital in Roehampton, and this was for just 11 people from 1997 to 2003. Techniques and rehabilitation schedules have changed since this time. It is likely that results of 20 cases of ITAP from the Stanmore centre in the UK will be published later this year. The expertise and volume of cases performed each year should be taken into account when considering where to commission this service.

Shorter time between operations and rehabilitation schedules such as from teams offering ILP in Germany and OGAP-OPL in Australia are an attractive option for both commissioning purposes and the individual. However neither centre have published details of effectiveness and so there is a lack of evidence on whether a shorter gap between surgeries and faster rehabilitation affects the osseointegration process, success of the procedure and long-term outcomes. The OPRA team from Sweden that favour a 12 to 18 month rehabilitation schedule timed from the first surgery remarked that in their experience "a rapid increase in implant loading can lead to implant loosening" and that "pain during rehabilitation can indicate overload and should be avoided". It was for these reasons

that they implemented their standard rehabilitation protocols in 1999. It is not clear why this is not also a concern where rapid rehabilitation is recommended with full weight-bearing in a matter of weeks.

There are lifelong cost and support issues to consider, such as the number of revisions that may be required, whether new models of implants, abutments and prostheses remain compatible and the outcomes for people in whom the procedure is unsuccessful.

15. Discussion and conclusions

The body of evidence regarding the effectiveness and safety of osseointegration remains small. There are just observational case series of 303 people who have undergone the procedure on 1 or both lower limbs. These studies variably compared quality of life before and after osseointegration and reported on complications and safety aspects of the procedure. Four low quality case series with comparisons to either socket users or people without limb loss were also available though they provide limited evidence due to methodological problems such as selection bias and unmatched groups. No randomised controlled trials were identified and there were no comparative studies of people with osseointegration implants compared to people who are unable to use socket prostheses. The main limitation of these case series is that with no matched control group we cannot be sure what the outcomes would have been if people had been given different types of osseointegration prostheses or if they had not undergone the procedure.

The studies reported on 111 cases of OPRA from single centres in Sweden (100 cases) and the UK (11 centres), and 102 cases of Endo-Exo Femur Prosthesis performed in Germany (69 cases) and The Netherlands (22 cases). Two conference abstracts reported on 101 cases of OPL performed in Australia. Follow-up times and outcome measures varied across these studies, limiting the ability to synthesise the results.

Effectiveness

Quality of life assessed using standard questionnaires after 1 or 2 years showed improvement for each technique (with varying levels of detail) though it stayed the same for a small proportion and worsened for a few cases. Mobility increased with a substantial number of people using the osseointegrated prosthesis on a daily basis. Due to the short length of follow up, changes in technique, improved design and small numbers of cases, it is not clear how long osseointegrated prostheses are likely to last. The longest time an Exo-Endo Femur Prosthesis is reported to have lasted is 12 years. For OPRA, there have been 3 cases lasting 10 years. There is very little data on the newer OPL technique from Australia and none on the latest OGAP-OPL model.

Safety

The procedure seems to be safe, with deep infections only affecting between 1% and 8% of cases and not all requiring implant removal. Newer techniques and changes in the titanium rod appeared to reduce the number of infections, though it is likely that superficial infections will continue to be a common occurrence. In these case series they occurred in between 32% and 96% of cases but were usually adequately treated with oral or intravenous antibiotics, though a large number of early cases required revision surgery. The overall removal rate was 8% to 20%, but reimplantation was successful in half of these cases. Pain remained severe 2 years after the first operation in 2% of cases and was

intermittent during rehabilitation in 10% of cases, but this was based on 1 case series. There was no available data on deaths associated with osseointegration.

Implant structure appears to be robust with only 1 reported structure failure. Bending or fracture of the abutment was more likely but this still occurred at a low frequency of just 9 cases. Bone fracture rate around the implant also appears to be very low at between 0% and 7% over up to 9 years. Implant stability was good up to 5 years but there were some bone structural changes such as cortical thinning, but no bone resorption.

From the available evidence, no procedure outshines the others in terms of safety.

Costs

There was little available evidence on which to base the cost-effectiveness of the procedure. Only 1 small cost-effectiveness study was identified which looked at the costs of a specialist prosthetic workshop in Sweden.

When considering costs associated with commissioning the procedure, the length between surgeries and rehabilitation costs are an obvious area of difference between OPRA and the other two techniques, Endo-Exo Femur Prosthesis (now called ILP) and OPL (now called OGAP-OPL). OPRA has the second operation after 6 months and a slow rehabilitation regime over the following 6 to 12 months while the others have a much shorter regime. However, there is much more detailed effectiveness data for OPRA than for the other techniques and this should be taken into account. Regardless of the type of procedure, there are lifelong cost and support issues to consider, such as the number of revisions that may be required, whether new models of implants, abutments and prostheses remain compatible and costs for people in whom the procedure is unsuccessful.

Candidates

As there is no data on outcomes if osseointegration is unsuccessful, it seems sensible for osseointegration to only be offered to people who have significant difficulties with the conventional socket technique, as applied by the majority of centres offering osseointegration. Most recipients of osseointegrated implants had amputations due to trauma or tumour, with a few cases due to infection but outcomes were not compared between these causes. All of the case series excluded people with amputation due to diabetes except for 2 cases of OPRA in the early years of the procedure because of concerns about wound healing and complications.

Gaps in the evidence

The studies did not split the effectiveness or safety outcomes according to the reason for amputation, or different types of trauma – for example blast injury versus surgical amputation. There was also no comparison of results according to variables such as age, weight or time since amputation.

No study reported on the outcomes for people for whom osseointegration was unsuccessful so it is not known if their situation was worse than before or not. This may be why most centres only perform the operation if there are major problems with the conventional socket prostheses.

No studies were found which compared the BMD of people with osseointegration implants and socket prosthesis users or wheelchair users. In theory, increased mobility should mean that more weight-bearing activity is possible which could improve bone mineral density and contribute to prevention of osteoporosis.

Future

When the ITAPTM study from the UK is published, hopefully later this year, there will be long-term follow details of up to 8 years for 20 patients. The ongoing OPRA study of 51 amputees from Sweden which started in 1999 will also provide longer follow-up in the future and is planned to continue until 2027. It will also be interesting to see the results of the randomised double-blind placebo controlled trial of whether Denusomab improves bone mineral density for people with osseointegrated prostheses which finishes this year.

Conclusion

In summary, low quality evidence indicates that osseointegration implants improves quality of life for the majority of recipients and appears to be a safe procedure with only small numbers affected by the most important potential complication of deep infection. With a lack of high quality evidence, osseointegration could be suitable for the NHS England Commissioning through Evaluation scheme (CtE)[3, 37], but there is insufficient evidence to recommend one technique over another. This is due in part to a lack of efficacy results for Endo-Exo Femur Prosthesis, little safety or efficacy data for OPL and none for ITAP. There are also no studies directly comparing the techniques. Any commissioning should include clinical governance, audit and standard assessments of long-term outcomes such as the Q-TFA and include all participants with no drop-outs or selective reporting so that this can better inform future decision-making.

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Appendix A: Scope

Table 3: Scope

Research questions:	Inclusions	Exclusions
P – Patients / Population Which patients or populations of patients are we interested in? How can they be best described? Are there subgroups that need to be considered?	Adult amputees. We will consider and describe the different populations included in the studies identified to determine which categories of patients are most likely to benefit, and in what circumstances, and in which patients it should be used. Examples of different population subgroups are those with traumatic amputations, poor vascular perfusion of the stump, bilateral amputations, different sites of lower leg amputation (through and above knee), those with poor fit of prosthesis using socket technologies.	Children Congenital conditions
I – Intervention Which intervention, treatment or approach should be used?	Osseointegration/ direct skeletal fixation. There are multiple techniques and the exact technique utilised in each study will be noted, including: • Associated Brånemark Osseointegration Centers – Osseointegrated Prostheses for the Rehabilitation of Amputees (OPRA) • Sana Clinics Lübeck – Endo-Exo Prosthesis • Stanmore Implants Ltd – Intraosseous transcutaneous amputation prosthesis (ITAP) • Osseointegration International – Osseointegration Prosthetic Limb (OPL) • DJO Global – Proprietary osseointegration technology	None
C – Comparator What is/are the main alternative/s to compare with the intervention being considered?	Active stump management involving multiple socket fitting and revision surgery Being a full time wheelchair user Standard method of attachment of prosthesis using sockets	None
O – Outcomes What is really important for the patient? Which outcomes should be considered? Examples include intermediate or short-term outcomes; mortality; morbidity and quality of life; treatment complications; adverse effects; rates of relapse; late morbidity and re-admission; return to work, physical and social functioning, resource use.	*Critical to decision-making:* • Quality of life: – Mobility – Confidence – Pain – Return to work/vocational outcomes • Complications of osseointegration procedures and their time course • Bone density • Value for money – Return on prosthetic investment – Costs of stump management – Risks of infection and complications there of – Reduced obesity, vascular disease and diabetes risk – Speed of return to work/normal activities of daily living	None

	Important to decision-making: • Where best performed: internationally, UK, England, regionally and number of teams • Skills needed • Convenience, cost, team experience	
Study designs	Any human study	Case series of less than five people Animal studies
Other parameters	Published since 2000 English language studies only OECD countries including Germany	Non-OECD countries

Appendix B: Search strategy

The search aimed to identify both academic, peer-reviewed articles, and grey literature documents from 2000 to January 2016 for literature specifically relating to osseointegrated prostheses. The searches did not include any study type restrictions or methodological filters as we aimed to identify all human studies including on-going trials and conference abstracts. No language restrictions were used. A 3-pronged approach was used for the search:

1. Biomedical databases
2. Speciality databases and grey literature
3. Supplemental search techniques

Biomedical databases searching

- MEDLINE (via Embase.com)
- Embase (via Embase.com)
- Cochrane Library
  - Central Register of Controlled Trials (CCTR)
  - Cochrane Database of Systematic Reviews (CDSR)
- Scopus (Elsevier)
- NICE Evidence
- TRIP database

Speciality databases and grey literature searching

- Google
- Google Scholar
- Clinicaltrials.gov
- Grey Literature Report
- Defense Technical Information Center (DTIC), US Department of Defense database
- The NARIC Knowledgebase (US National Rehabilitation Information Center)
- CIRRIE Database of International Rehabilitation Research (Index to published research conducted outside of the United States) and REHABDATA (for US research)
- PEDro (Physiotherapy Evidence Database)

Supplemental searching

In addition to database and grey literature searches, we have also used supplemental searching, including the use of 'pearl growing' methods such as author searching and reference harvesting. Highly relevant documents identified from databases and the grey literature will be used as 'pearls' for these supplemental methods.

Search/sifting results

Table 4: Sift results

Databases and sites searched	Dates searched	Number of hits
MEDLINE & Embase	2000-11/01/2016	459
Cochrane Database Syst Rev	2000-11/01/2016	0
Cochrane CENTRAL	2000-11/01/2016	2
Scopus	2000-2016	471
TRIP database	12/01/2016	0
Speciality & grey literature databases	20/01/2016	108
Clinicaltrials.gov	20/01/2016	2
Non-database searching/Supplemental searches	19/01/2016	8
Total number of hits		1040
Total number after de-duplication		749
Total number after first appraisal		86
Total number appraised at full text		29
Total number included in review		24

Record of searches strategies

MEDLINE & Embase (Embase.com)

#1 'bone regeneration'/de
#2 osseointegration:ab,ti OR osseointegrat*:ab,ti OR osseoanchor*:ab,ti OR intraosse*:ab,ti
#3 (osseo NEXT/2 integrat*):ab,ti
#4 opra:ab,ti OR opl:ab,ti OR itap:ab,ti
#5 implant:ab,ti AND (anchor*:ab,ti OR **fixat*:ab,ti OR transcut*:ab,ti OR transderm*:ab,ti**)
#6 #1 OR #2 OR #3 OR #4 OR #5
#7 'amputation'/exp
#8 amput*:ab,ti
#9 'limb prosthesis'/exp
#10 limb:ab,ti AND (artificial:ab,ti OR prosthe*:ab,ti)
#11 #7 OR #8 OR #9 OR #10
#12 #6 AND #11
#13 #6 AND #11 AND [2000-2016]/py

Cochrane Library - Cochrane Database of Systematic reviews, CENTRAL, HTA, NHS EED, DARE

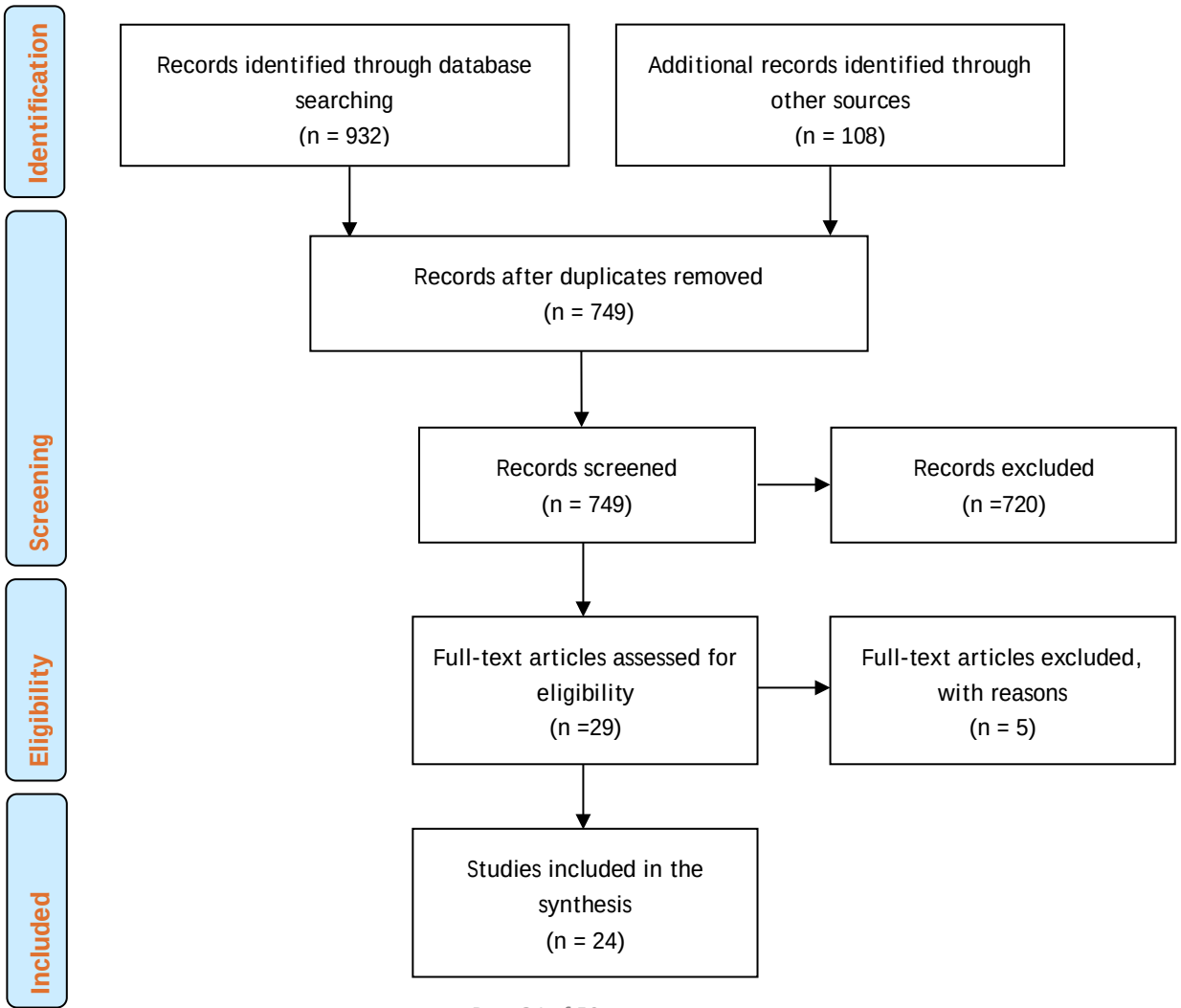
#1 MeSH descriptor: [Osseointegration] this term only
#2 "Bone Regeneration":ti,ab,kw
#3 (osseointegrat* or osseoanchor* or intraosse*):ti,ab,kw
#4 (osseo next/2 integrat*):ti,ab
#5 (opra or opl or itap):ti,ab
#6 (implant and (anchor* or fixat* or transcut* or transderm*)):ti,ab
#7 #1 or #2 or #3 or #4 or #5 or #6

#8 **MeSH descriptor: [Amputation] explode all trees**
#9 MeSH descriptor: [Amputation, Traumatic] this term only
#10 MeSH descriptor: [Amputation Stumps] this term only
#11 **MeSH descriptor: [Amputees] this term only**
#12 **amput*:ti,ab**
#13 **MeSH descriptor: [Artificial Limbs] this term only**
#14 **(limb and (artificial or prosthe*)):ti,ab**
#15 **#8 or #9 or #10 or #11 or #12 or 13 or 14**
#14 **#7 and #15**

Scopus

((TITLE-ABS-KEY (osseointegrat* OR osseoanchor* OR "bone regeneration")) OR (TITLE-ABS-KEY (osseo integrat*)) OR (TITLE-ABS-KEY (intraosse* OR opra OR opl OR itap)) OR (TITLE-ABS-KEY (implant AND (anchor* OR fixat* OR transcut* OR transderm*)))) AND ((TITLE-ABS-KEY (amput* OR (limb AND (artificial OR prosthe)))) OR (INDEXTERMS (amputation))) AND (LIMIT-TO (PUBYEAR 2000 - 2015)

PRISMA 2009 Flow Diagram



Appendix C: Excluded studies at full text

Table 5: Studies excluded at full text

Author	Title	Reason for exclusion
Isaacson 2009[38]	Bioelectric analyses of an osseointegrated intelligent implant design system for amputees	Proof of concept modelling study
Isaacson 2010[39]	Developing a quantitative measurement system for assessing heterotopic ossification and monitoring the bioelectric metrics from electrically induced osseointegration in the residual limb of service members	Modelling laboratory study
Lundberg 2011[40]	My prosthesis as a part of me: A qualitative analysis of living with an osseointegrated prosthetic limb	Qualitative and purposive
Pantall 2013[41]	Muscle activity during stance phase of walking: Comparison of males with transfemoral amputation with osseointegrated fixations to nondisabled male volunteers	Able-bodied control
Webster 2009[42]	Perceptions and acceptance of osseointegration among individuals with lower limb amputations: A prospective survey study	Survey of people without osseointegration implant

Appendix D: Data extraction table

Table 6: Data extraction table

Study	Country	Participants	Intervention	Outcomes	Author's conclusions	Comments/ limitations
Juhnke 2015[36] Retrospective case series 1999 to 2013 Single centre Single surgeon	**Germany**	**69 transfemoral amputees (56 males)** 4 had bilateral implants Average age at amputation: 34.5±14.2 years (range 14 to 76 years) Average age at implantation: 45.4±12.3 years (range 17 to 76 years) Participants were selected to minimise infection risk, so were amputees due to: • Trauma from RTAs	**Endo-Exo Femur Prosthesis, later termed Integral-Leg-Prosthesis (ILP)** Two-stage procedure – first debulking soft tissue, addressing any burns and then implanting device into bone and closing skin for internal healing and osseointegration. After 6 weeks, opening skin and attaching bridging connector. 2nd generation cephalosporin given for each surgery. Group 1: N=30 (Design A, N=21 and Design B, N=9 from 1999 to 2008)	**Group 1 up to 14 years follow-up, Group 2 up to 5 years** **Efficacy** Implants have so far lasted up to 12 years. **Safety** There were 104 revisions or unplanned interventions. Revision surgery for infection: • Group 1: 23 (77%) • Group 2: 0 (0%) • Absolute risk	"The early high rate of reoperation, which was seen with the initial design iterations, is not a valid criterion for abandoning skeletal prosthetic docking."	Single surgeon and centre, unclear how great an impact this has on results. Interim data was published as: Aschoff 2012[29], Aschoff 2011[30] (of the first 39 patients, 37 said they would do it again), Aschoff 2010[31], Aschoff 2009[32] (reports that 16 to 18cm of femur is needed. Reports on 30 cases and is only available in German).

Study	Country	Participants	Intervention	Outcomes	Author's conclusions	Comments/ limitations
		(N=51) • Tumour (N=7) • Infected total knee arthroscopy (N=3) • 4th degree burn (N=1) • Other (N=7) They were assessed to be emotionally and intellectually able to undergo rehabilitation and lifelong stoma wound care and hygiene. Exclusion criteria: • Dysvascular and atrophic bone conditions • Immunosuppression • Chemotherapy • Diabetes • Atherosclerotic peripheral vascular	Group 2: N=39 (Design C from 2009 to 2013) Design A: endomodule, bridging connector and bracket. Design B: structured surface of distal section of endomodule was removed as it was abrasive to skin and soft tissue rather than encouraging skin to attach to the device. Bridging connector was slimmer and bracket smaller. Design C: no bracket, bridging connector shortened, coating with non-abrasive titanium niobium oxynitride ceramic. Thinning of subcutaneous fat to 2cm so that there was a reduced length of skin in contact with the bone capping	reduction of Design C for early soft tissue infection before 6 months ARR 42% (95% confidence interval [CI] 25 to 59, p<0.001) • ARR for late soft tissue infection for Design C 55% (95% CI 35 to 82, p<0.001) Removal due to failure to osseointegrate: • Group 1: 4 (13%), 2 reimplanted • Group 2: 0 (0%) Fractures: • Group 1: 3 (10%) 4,5 and 6 months		Further studies reporting similar results for these patients are: Aschoff 2014[27] (Abstract only published, 71 implantations over 1999 to 2013, with 7 fractures). Aschoff 2014[28] (Abstract only published, "overall patient's satisfaction with their prosthesis is high". "Vital to the success of this new technique is a close relationship and cooperation between surgeon, company, prosthetist, rehab facilities, GP, security system and patient for life.")

Study	Country	Participants	Intervention	Outcomes	Author's conclusions	Comments/ limitations
		disease • Skeletal immaturity • Poor bone quality (bone damaged by radiation therapy, metabolic bone disease, renal insufficiency and/or dialysis) • People satisfied with conventional socket prosthesis	portion of the implant to reduce infection risk. Larger channel made in second operation as a tight seal caused retained haematoma and serous fluids in Group 1 which could lead to failure. A 3mm gap gave good drainage. Post-op care: • Twice daily cleaning with mild soap and water • Partial weight-bearing after surgery • Full weight-bearing after 4 to 6 weeks without crutches	after implantation • Group 2: 2 (5%) 31 and 34 months after implantation, fixed with screws Implant structure failure: • Group 1: 1 (3%) at 7 years • Group 2: 0 (0%) Any unplanned surgical intervention: • Group 1: 24 (80%) • Group 2: 5 (12.8%), (included 1 to remove excess granulation tissue, 1 prolonged process		Group 2 have had less time for complications to occur. Very little data on efficacy outcomes.

Study	Country	Participants	Intervention	Outcomes	Author's conclusions	Comments/ limitations
				of lengthening residual femur which ended up with a fistula over the greater trochanter which continues to secrete and a dressing is changed twice per day (patient can walk with a stick) and 1 revision due to non-osseointegration after a different surgeon performed the original op). 1 case of intramedullary		

Study	Country	Participants	Intervention	Outcomes	Author's conclusions	Comments/ limitations
				infection in Group 1. Patient had osteosarcoma and skeletal immaturity. Osseointegration was inadequate, leading to movement of the rod and infection.		
Al Muderis 2015[33] Prospective case series Australia 2011 to 2013 The Netherlands 2009 to 2011 Single centre University hospital in each country	**Australia** **The Netherlands** (Australia N=22, The Netherlands N=24)	**46 transfemoral amputees** 3 had bilateral implants Average age at amputation or implantation: NR Inclusion and exclusion criteria: NR	**OPL or Endo-Exo Femur Prosthesis**	**2 year follow-up** **Safety** Soft tissue infection (cellulitis): • 22 required oral antibiotics (7 Australia, 15 The Netherlands) • 13 required surgical intervention (5 Australia, 8 The Netherlands) Osteitis:	"Complications related to the osseointegrated leg-prosthesis do occur but the suffering and disabilities are relatively mild. Infectious events are superficial and can be managed with intensive local irrigation and antibiotics. Strict patient selection and adherence to	No further details supplied. Abstract only published. No efficacy details provided. Covers the Van de Meent 2013[15] Netherlands study – giving an extra year of follow-up, and some cases from the Khemka 2015[34, 35] Australia case studies.

Study	Country	Participants	Intervention	Outcomes	Author's conclusions	Comments/ limitations
				• 1 (The Netherlands) Implant failure/ Osteomyelitis: • 1 (Australia)	exclusion criteria, may reduce complication rate."	
Brånemark 2014[8] Prospective case series of consecutive cases 1999 to 2007 Single centre	**Sweden** (Amputees from UK (N=1), Sweden (N=25), Norway (N=14), Spain (N=11))	**51 transfemoral amputees** 6 bilateral (4 had the procedure on both sides in this study, 1 had already had an OPRA fitted and 1 had too small a stump), 45 unilateral Average age at amputation: 32 years (range 13 to 64 years) Average age at implantation: 44 years (range 20 to 65 years) Amputations due to:	**Osseointegrated Prostheses for the Rehabilitation of Amputees (OPRA)** Two-stage procedure – first operation to insert fixture into the bone, then closing the skin. After 6 months, second operation which divides the muscles, sutures them to the periosteum leaving 5mm bare bone covered by part of a skin flap which has had subcutaneous fat removed. Abutment is fitted to the fixture.	**2 year follow up** **Efficacy** 92% of the implants survived to 24 months. Questionnaire for Persons with a Transfemoral Amputation (Q-TFA): • Mean prosthetic use score increased from 47 to 79 (0 to 100), p<0.001 • Mean prosthetic mobility score increased from 52	"The high cumulative survival rate at two years (92%) combined with enhanced prosthetic use and mobility, fewer problems and improved quality of life, supports the 'revolutionary change' that patients with TFA have reported following treatment with osseointegrated percutaneous	6 people did not complete the questionnaires as they withdrew from the study – 3 due to implant removal, 1 death, 1 lost to follow-up and 1 due to injury of the other leg. Limitations: Small study size Single centre Non-randomised Further detail on 39 of the 45 unilateral amputees from this study is provided by Hagberg 2014[17].

Study	Country	Participants	Intervention	Outcomes	Author's conclusions	Comments/ limitations
		• trauma (N=33) • tumour (N=12) • other (N=6) 42 used socket-suspended prostheses. 8 were unable to obtain comfortable prostheses and 1 had too small a stump. Exclusion criteria: • Age <20 or >70 • Severe peripheral vascular disease • Diabetes • Skin disease affecting amputation • Systemic corticosteroids • Chemotherapy • Pregnancy • Skeletal immaturity		to 70, p<0.001 • Mean problem score reduced from 44 to 17, p<0.001 • Mean global score increased from 38 to 77, p<0.001 Short-Form (SF)-36: • Physical function improved from 35 to 58, p<0.001 • Role-physical improved from 41 to 63, p<0.001 • Other parameters did not change significantly Other outcomes • 40/45 had daily prosthetic use	prostheses."	Previous publications reported on smaller numbers of the OPRA study such as the first 18 patients in Hagberg 2008[18] and 100 patients including the 51 in Hagberg 2009[9] but going back to 1990. In 2009, 9/14 people were still using an implant that had been inserted in 1990-1994, though 6 had been reimplanted. Tillander 2010[25] included 33 of them in a study on infectious complications which are reported here.

Study	Country	Participants	Intervention	Outcomes	Author's conclusions	Comments/ limitations
		• Likely inability to comply with treatment and follow-up • No current problems with prosthesis		compared with 29/51 before • 1 no use due to pain, 4 less than daily use • Overall situation improved for 31/45 (69%) of people, stayed the same for 11/45 (24%) and got worse for 3 (7%) **Safety** Death: • 1 unrelated to the implant Superficial infection: • 41 times in 28 people (infection rate 54.9%) treated with		Nebergall 2012[22] analysed bone changes and implant stability.

Study	Country	Participants	Intervention	Outcomes	Author's conclusions	Comments/ limitations
				antibiotics – 4 in hospital. Deep infection: • 1 led to loosening and removal • 1 treated with oral antibiotic • 2 had positive cultures at surgery with no signs of infection. Treated with antibiotics for 6 months Removal of implant: • 1 due to infection • 3 due to aseptic loosening which caused pain on weight-bearing Pain: • Almost constant for 1 person by 2		

Study	Country	Participants	Intervention	Outcomes	Author's conclusions	Comments/ limitations
				years post-op which showed loosening 4 months later • 5 had episodic pain during rehabilitation 5 fractures in 4 people: • 3 ipsilateral hip • 1 below elbow • 1 vertebral compression Mechanical complications of abutment: • 9 fractures or bending of the abutment or screw (6 occurred in 1 person). All were fixed.		
Hagberg 2009[9]	**Sweden**	**100 transfemoral amputees (61 males)**	**OPRA**	**Up to 17.5 years follow up**	"A rapid increase in implant loading can	Includes 51 people from the OPRA study.

Study	Country	Participants	Intervention	Outcomes	Author's conclusions	Comments/ limitations
Retrospective case series 1990 and 2008		6 had bilateral implants (all cases of trauma) Average age at amputation: 32±13.9 years (range 10 to 63 years) Average age at implantation: NR Years since amputation when implanted 11.5±11 years (range 0 to 44 years) Reason for amputation: • Trauma (N=67) • Tumour (N=21) • Infection (N=7) • Vascular including embolus (N=3) • Diabetes (N=2) 74 people used a socket	Two stage surgery – first stage implantation, second stage 6 months later to attach the abutment and perform soft tissue surgery followed by immobilisation for 10 to 12 days. OPRA rehabilitation protocol instituted in 1999. **Rehabilitation regimes:** • Normal speed protocol – about 12 months from first surgery • Half speed protocol – about 18 months from first surgery	**Efficacy** 68 people with 74 implants were using osseointegrated prostheses (all 6 with bilateral implants were using them). **Safety:** Reason 32 not using: • 4 deceased • 7 due for second surgery • 6 initial training • 1 osteomyelitis • 2 severe phantom limb pain • 1 contralateral limb pain • 20 implants removed: – 13 retreated, of	lead to implant loosening…pain during rehabilitation can indicate overload and should be avoided."	

Study	Country	Participants	Intervention	Outcomes	Author's conclusions	Comments/ limitations
		prosthesis on at least 1 day a week Exclusions: • Severe vascular disease • Ongoing chemotherapy • Immunosuppressive medications • Growing children • Adults over 70		which 9 were successful – 11 implants permanently removed		
Haggstrom 2013[21] Retrospective cost analysis 1993 to 2008 Single centre visits and survey questionnaire	**Sweden**	**50 people with unilateral transfemoral amputation** Workshop attendance (N=20 osseointegrated prostheses, N=36 socket-suspended prostheses, N=6 with both) Inclusion criteria: • All prosthetic service performed exclusively at this workshop during the time period.	**OPRA** Prosthetic costs from attendance at a prosthetic workshop from 1993 to 2008. "Prostheses" was all external elements. Includes: • Salaries • New prostheses • Services • Repairs • Adjustments • Maintenance	**Cost** Total prosthetic mean cost/year: • €3,672±2259 Socket prostheses • €3149±1682 osseointegrated prostheses Mean number of visits/year to a workshop: • 7.2±4.2 socket	"Despite significantly fewer visits for prosthetic service the annual mean costs for osseointegrated prostheses were comparable with socket-suspended prostheses. This study suggests it is due to more advanced prosthetic	Costs associated with initial surgery were not included in this analysis. No clinic appointments were included or other health-related costs. The 2 groups were not matched. Costs are estimated for 1 Swedish clinic in Euros based at 2009 prices. This

Study	Country	Participants	Intervention	Outcomes	Author's conclusions	Comments/ limitations
		Exclusion criteria, amputation due to: • Diabetes • Atherosclerosis		prostheses • 3.1±1.5 osseointegrated prostheses Average cost to manufacture a new prostheses in 2009: • €4,890±1758 Socket prostheses • €9370±6441 osseointegrated prostheses	components being used with osseointegrated prostheses."	may be very different to UK prices in 2016.
Khemka 2015[34] Prospective case series 2011 to 2014 Single centre	**Australia**	**16 transfemoral amputees** Average age at amputation: NR Average age at implantation: 51±12 years Cause of amputation: • Trauma (N=11)	**Osseointegrated Prosthetic Limb (OPL)** The Q-TFA was completed 1 year before surgery and between 6.5 and 24 months after Stage 1 surgery for osseointegration.	**2 year follow up** **Efficacy** Q-TFA • Mean prosthetic use score increased from 63 to 91 (56% reported an improvement)	"The average results demonstrated an improvement in each domain, particularly in the reduction of problems and an increase in global state."	Abstract only published. Safety data was published for 2 years post-op by Al-Muderis 2015[33].

Study	Country	Participants	Intervention	Outcomes	Author's conclusions	Comments/ limitations
		• Congenital (N=5) 12 used a prosthesis and 4 were wheelchair-bound		• Mean prosthetic mobility score increased from 64 to 82 (75% reported an improvement) • Mean problem score reduced from 40 to 8 (94% reported an improvement) • Mean global score increased from 47 to 79 (69% reported an improvement)	"These results were comparable to previous studies relying of screwed fixation confirming that press-fit implantation is a viable alternative for bone-anchored prostheses."	
Khemka 2015[35] Prospective case series Single centre Single surgeon	**Australia**	**101 people with lower leg amputation** 7 bilateral implants Average age at amputation: 33 (range 3 to 76 years)	**Osseointegrated Prosthetic Limb (OPL)** Above and below knee interventions, N=NR	**Follow-up period NR** **Efficacy** Health Related Quality of Life questionnaires (Q-TFA and SF 36): • "Improved	"This study shows favourable results for OPL treatment for above knee as well as below knee amputees, compared to Socket	Abstract only published. Single surgeon and centre, unclear how great an impact this has on results.

Study	Country	Participants	Intervention	Outcomes	Author's conclusions	Comments/ limitations
		Average age at implantation 44.3 (range 17 to 76 years) Cause of amputation: • Trauma (N=77) • Infection (N=12) • Tumour (N=10) 30% wheelchair-bound		dramatically" K scores: • "significant improvement" p=0.0006 Time Up and Go and 6MWT test: • "significant improvement" p=0.0149 Energy expenditure: • Increased 4-fold **Safety** "Low rate of complications"	prosthesis. Our experience of over 100 patients has revealed encouraging results with a major improvement in patient's functionality and quality of life, and a low rate of complications."	Figures inaccurate. Reporting of actual results very poor.
Nebergall 2012[22] Prospective case series	**Sweden**	**51 transfemoral amputees** 6 bilateral (4 had the procedure on both sides)	**OPRA** Long-term fixation and stability of the osseointegrated implant using	**Up to 10 year follow up** **Safety**	"The RSA analysis for the OPRA system indicates stable fixation of the	Same case series as reported by Brånemark 2014[8].

Study	Country	Participants	Intervention	Outcomes	Author's conclusions	Comments/ limitations
1999 to 2007 Single centre		Average age at amputation: NR Average age at implantation: 45 years (range 21 to 65 years)	radiostereometric analysis (RSA) and periprosthetic bone remodelling on plain X-rays, both performed at 6 months, 1,2,5,7 and 10 years after surgery. 15 implants were analysed at 5 years, 3 implants at 10 years (due to the small number these were not reported).	Median migration of the implant at 5 years: • -0.02mm distally Rotational movement of the implant at 5 years: • 0.42º around the longitudinal axis Cancellization of the cortex: • In at least 1 zone in over half of patients by 1 year • Affected many cases in year 2 • Reduced by year 5 Cortical thinning: • Zones 1 to 12, but mainly in the distal zones at the 5-year follow-	implant… bone remodelling showed similarities with changes seen around uncemented hip stems."	Small number of implants analysed at 5 years.

Study	Country	Participants	Intervention	Outcomes	Author's conclusions	Comments/ limitations
				up.		
Sullivan 2003[14] Retrospective case series of all recipients 1997 to 2003 Single centre at Queen Mary's Hospital Roehampton	**UK**	**11 transfemoral amputees** (from 56 potential candidates) Average age at amputation: NR Average age at implantation: NR Inclusion criteria: • Unable to use socket technique • Full skeletal maturity • Less than 100kg Exclusion criteria: • 70 years old and over • Osteoporosis • Hip limitations (osteoarthritis, flexion	**OPRA** Two stage procedure. Implant and then abutment 6 months later. Rehabilitation: Six weeks afterwards a small training prosthesis is attached. Two to 3 months of training are required before full body weight can be put onto prosthesis. Then 3 months of using 2 crutches. 18 months from the first surgical procedure.	**6 year follow up** **Efficacy** 9 using the osseointegrated prosthesis daily – 1 for 5.5 years. 5 had the abutment replaced after falls. Quality of life: • Negative aspects: – Longer rehab than expected – High number of visits for rehab – Slowness of rehab program • Positive aspects: – Improved proprioception – Ability to walk	Quality of life improved for the participants who completed the program. There were some concerns about infection, abutment damage and length of rehabilitation.	Small study, limited length of follow-up. No details on outcomes for the 2 people who had the implant removed.

Study	Country	Participants	Intervention	Outcomes	Author's conclusions	Comments/ limitations
		contractures) • Social and psychological factors • Medical conditions that would add risk to the procedure • Reluctance to comply with protocol		further and do more – No longer felt disabled, were able to participate with full daily living and activities such as cycling. **Safety** 2 had implant removal due to infection after 1 year.		
Van de Meent 2014[15] Prospective case series 2009 and 2011 Single centre	**The Netherlands**	**22 transfemoral amputees (18 males)** 1 bilateral amputee. Mean age 46.5 (range 23 to 67 years) Average time since	**Endo-Exo Femur Prosthesis** Two step surgery. First step, residual femur shortened to 20cm above contralateral knee joint space. Second operation after 6 weeks. Rehabilitation:	**1 year follow up** **Efficacy** Q-TFA: • Global score increased from 39 to 63 Prosthesis use:	"Osseointegration is a suitable intervention for individuals with transfemoral amputation because of trauma or tumour, who have reduced prosthesis	Limited data on safety and adverse effects as only 1 year follow-up. 2 year follow-up safety data reported by Al Muderis 2015[33].

Study	Country	Participants	Intervention	Outcomes	Author's conclusions	Comments/ limitations
		amputation 16.4 years (range 2 to 45 years) Cause of amputation: • Trauma N=20 • Tumour N=2 Inclusion criteria: • Significant socket related problems affecting quality of life Exclusion criteria: • Femur <8cm • Amputations due to diabetes or vascular disease • Severe cognitive disorders • Severe psychiatric disorders	Two weeks after second operation weight-bearing exercises began using a short pylon, with up to 50% of weight. Full weight-bearing in second week. Full length prosthesis attached in week 4, with full weight bearing over the next 2 weeks. Average rehab program was 6 to 8 weeks.	• Increased from 56 to 101 hours/week 6 minute walk test (6MWT): • Increased from 321m to 423m Timed Up & Go test (TUG): • Improved from 15.1 seconds to 8.1 seconds Oxygen consumption: • Reduced from 1330mL/min to 1093mL/min **Safety** 8 mild soft tissue infections treated with	use as a result of socket-related residual limb/skin problems. OIP [Endo-Exo Femur Prosthesis] significantly increased walking ability and prosthesis-related quality of life.	

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				intensive cleaning with hydrogen peroxide and sometimes antibiotics. No deep tissue infections or osteomyelitis or implant failures.		
Frossard 2010[24] Case series with control groups	**Unclear – Australia/Sweden**	**12 people with osseointegrated implant** Unilateral transfemoral amputation and osseointegrated fixation for at least 1 year and able to walk unaided at least 200m. 9 men, 3 women Average age at amputation or implantation: NR Inclusion and exclusion	**Osseointegrated implant not further specified** Gait analysis compared to data sets from the literature for 142 people with transfemoral amputation fitted with a socket, and 258 able-bodied participants.	**1 year or more post op** **Efficacy** Cadence: • 46 strides /minute, 2% faster than socket and 11% slower than able-bodied. Duration of gait cycle: • 1.29 seconds, 3% shorter than socket and 9%	"All combined, the results indicated that the fitting of an osseointegrated fixation has enabled this group of amputees to restore their locomotion with a highly functional level. Further longitudinal and cross-sectional studies would be required to confirm these outcomes.	Study biased towards recruitment of people with successful implants. Not a case control study as there was no attempt to get a matched control group in terms of demographics, conditions or level of disability. "Controls" were able to use their socket prosthesis whereas this was the reason people had osseointegrated

Study	Country	Participants	Intervention	Outcomes	Author's conclusions	Comments/ limitations
		criteria: NR		longer than able-bodied. Swing phase of the gait cycle was longer than the support phase (43% of the gait cycle was for swing, and 57% for support) compared to socket (41% swing, 59% support) and able-bodied (38% swing, 62% support).		implants, or healthy people without limb loss.
Hagberg 2005[19] Case series with a control group Surgery performed before 1999 Multiple centres	**Sweden and UK**	**20 people with osseointegrated implant** Implant for at least 2 years and able to walk for at least 100m (N=20). Socket prosthesis users in Sweden (N=43).	**OPRA** Measurement of hip range of motion with and without prosthesis using a goniometer and self-reported discomfort when sitting.	**2 years follow up or more** **Efficacy** Hip range of motion: • No restriction for osseointegrated prosthesis group (none had less than 90° hip	Socket prostheses reduce hip range of movement and can cause discomfort when sitting. Osseointegrated prostheses do not restrict hip range of movement and are less likely to cause	Selection bias. Not a case control study as there was no attempt to get a matched control group in terms of demographics, conditions or level of disability. "Controls" were able to use their socket

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		Average age at amputation or implantation: NR Exclusion: Vascular amputees		flexion) • Reduced in all directions with socket prosthesis (37% had less than 90° hip flexion) Sitting discomfort: • 5% of the osseointegrated group compared to 44% of the socket group	discomfort when sitting.	prosthesis whereas this was the reason people had osseointegrated implants.
Häggstrom 2013[20] Case series with control group 1998 to 2007	**Sweden**	**34 transfemoral amputees** 17 assessed before and 2 years after osseointegration implant. Average age at amputation or implantation: NR Cause of amputation:	**OPRA** Vibrotactile evaluation using a vibrator pin on the soul of the prosthetic foot and intact foot using different frequencies.	**2 year follow-up** **Efficacy** Vibrotactile • Detection threshold improved by 10 Decibels (Db) for high frequencies of 125Hz and	Improved detection of high frequency vibrations may lead to advantages in gait control.	Performed sitting down because participants were not able to stand still and do the test which lasted longer than 30 minutes. Ten of the osseointegrated group had the same knee components of their prostheses in the follow-

Study	Country	Participants	Intervention	Outcomes	Author's conclusions	Comments/ limitations
		• Trauma (N=11) • Tumour (N=6) 17 'controls' with socket prostheses evaluated once. **Exclusion:** • Amputations due to diabetes • Arteriosclerosis		250Hz (from 110Db to 100Db for 125Hz and from 122Db to 111Db for 250Hz). • There was no change for lower frequencies of 8Hz, 16Hz, 32Hz and 64Hz. • These results were better than for the control group.		up tests. Not a case control study as there was no attempt to get a matched control group in terms of demographics, conditions or level of disability. "Controls" were able to use their socket prosthesis whereas this was the reason people had osseointegrated implants.
Tranberg 2011[23] Case series with a control group 1998 to 2007 Single centre	**Sweden**	**19 transfemoral amputees** Gait analysis before and 2 years after osseointegration (N=19) compared to healthy controls (N=57). Average age at amputation or implantation: NR	**OPRA** 3-dimensional gait analysis	**2 year follow up** **Efficacy** Hip extension: • Increased by 7.3° from -2.6°(range -13.4° to 10.7°) to -9.9°(range -29 .4° to 5°),	Osseointegration provides significant changes in kinematic pattern and even though they were moderate, they may in the long-term have a positive	No results were provided for the healthy "controls". Small sample size. Though the results were statistically significant, it is not clear if they were clinically significant.

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		Inclusion and exclusion criteria: NR		p=0.007. • This was an improvement towards the healthy controls (data not provided). Pelvic tilt: • Anterior pelvic tilt reduced by 4° from 21.7° (range 11.9° to 34.8°) to 17.7° (range 5.5° to 25.7°), p=0.016. • This was an improvement towards the healthy controls (data not provided).	influence on the lower back.	Not a case control study as there was no attempt to get a matched control group in terms of demographics, conditions or level of disability. "Controls" were adults without limb loss.