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Hand transplantation following amputation due to non-malignant indications

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Hand transplantation following amputation due to non-malignant indications [Handtransplantation efter amputation på grund av icke-malign orsak]

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Regional activity-based HTA 2016:91

Table of contents

1. Abstract

***Background*:** Bilateral upper extremity amputation is a devastating consequence of a traumatic or medical event that tremendously affects the life of a person both functionally and psychologically. Most daily life activities are severely impeded and personal assistance is required. The recommended treatment for upper limb amputees in Sweden is prosthetic replacement using either standard or osseointegrated prosthesis. No other treatment is thus far available for Swedish patients who cannot use a prosthesis. Hand transplantation is available in some countries (e.g. USA, France, Poland) and several health care centres consider it a valuable option particularly for bilateral amputees after a period of at least six months of failed attempt to use prostheses.

***Objective*:** To evaluate upper extremity transplantation in adults with hand/upper extremity amputation (non-malignant causes), for decision support for introduction of bilateral upper extremity transplantation in Region Västra Götaland.

***Search methods and study selection criteria*:** Systematic literature searches were performed (April 2016) in Medline, Embase, the Cochrane Library, Cinahl, AMED, PsycInfo and a number of HTA-databases. Case series were included because of a lack of controlled studies and since data on the natural course of upper extremity amputation was considered a representative alternative for no intervention. The certainty of evidence was defined according to GRADE. Grading the certainty of evidence for the case series started at GRADE ⊕◯◯◯.

***Main results*:** Six case series, five systematic reviews (SR) and one health economy study met the inclusion criteria. The SRs and the health economy study were only commented. All the included case series had study limitations (e.g. poorly described co-interventions, different amputation levels, retrospective analyses). Precision was poor due to few cases, but a clear effect was observed compared with no transplantation.. **Health-related quality of life** (HRQoL) was reported in two case series with a total of 10 patients, using Satisfaction with Life Scale or SF-36. The improvement was >2-fold. **Activities of daily living** (ADL) was studied in two case series with a total of 16 patients. Following transplantation the mean ability to easily perform 65 ADL tasks improved >2-fold, and complete failure to perform tasks decreased >5-fold. In one study (n=11) all patients were able postoperatively to perform daily tasks, with no further specification. **Hand motor- and sensory function** were overall functionally acceptable as measured with one or several validated tests. Seven out of ten patients **returned to work**, or similar activity.

Risks and complications: No fatalities were reported. Graft loss was reported in four case series with follow-up ranging from 6 months to 12 years. In one of three case series, one rejection resulting in graft loss (16%) occurred within the first year after transplantation. In a Chinese case series, graft loss related to poor compliance to immunosuppressive treatment was reported in seven (64%) out of 11 cases. Other complications were reported in four case series (n=27). Serious complications were common with frequent infectious complications, including reactivation of latent viral infections and opportunistic bacterial infections. All recipients had at least one acute rejection episode. Transient hyperglycaemia was common, as were vascular complications. As for other organ transplantations, late adverse effects such as increased risk of malignancies are to be expected.

***Concluding remarks*:** Upper extremity transplantation in adults with hand/upper extremity amputation (non-malignant causes) probably improves ADL, probably provides useful hand motor and sensory functions (moderate certainty of evidence, GRADE ⊕⊕⊕◯) and may improve HRQoL and ability to return to work (low certainty of evidence, GRADE ⊕⊕◯◯). Serious complications are common and need to be considered and thoroughly discussed with the patient before transplantation. Further and larger studies with long-term follow-up are needed.

2. Svensk sammanfattning – Swedish summary

***Bakgrund*:** Bilateral amputation av övre extremiteterna är en katastrofal händelse både funktionellt och psykologiskt. De flesta aktiviteter i det dagliga livet försvåras eller omöjliggörs och personlig assistans är nödvändig. I Sverige behandlas individer med amputerad övre extremitet med en hyls- eller osseointegrerad protes. För patienter som inte kan använda en protes finns idag ingen alternativ behandling tillgänglig. Handtransplantation används i några länder (t ex USA, Frankrike, Polen) och anses där vara ett värdefullt behandlingsalternativ, särskilt för bilateralt amputerade efter minst sex månaders misslyckade försök att använda protes.

***Syfte*:** Att utvärdera transplantation av övre extremitet hos vuxna som amputerats av icke-maligna orsaker, som beslutsunderlag för införande av bilateral handtransplantation i Västra Götalandsregionen.

Metod: Systematisk litteratursökning utfördes (april 2016) i Medline, Embase, Cochrane Library, Cinahl, Amed, PsycInfo och ett antal HTA-databaser. Fallserier inkluderades då kontrollerade studier saknades och eftersom naturalförloppet är välkänt och oföränderligt. Det vetenskapliga underlaget bedömdes enligt GRADE, där fallserier börjar på den lägsta nivån av GRADE (⊕◯◯◯).

***Resultat*:** Sex fallserier, fem systematiska översikter (SR) och en hälsoekonomisk studie uppfyllde inklusionskriterierna. De systematiska översikterna och den hälsoekonomiska studien kommenterades enbart. Samtliga fallserier hade begränsningar i studiekvalitet (bristfällig beskrivning av andra erforderliga behandlingsåtgärder, olika amputationsnivåer, retrospektiva analyser). Precisionen var låg på grund av få patienter, men effekten av transplantationen var uppenbar. **Hälsorelaterad livskvalitet** (HRQoL), med Satisfaction with Life Scale eller SF-36, rapporterades i två fallserier med totalt 10 patienter. Förbättringarna var >2-faldiga. **Allmän daglig livsföring** (ADL) studerades i två fallserier med totalt 16 patienter. Efter transplantation förbättrades förmågan att enkelt utföra 65ADL uppgifter >2-faldigt, och misslyckandefrekvensen minskade >5-faldigt. I en annan studie (n=11) rapporterades att samtliga patienter postoperativt kunde utföra dagliga uppgifter, utan närmare specifikation. **Handmotorik och -sensorik** var vanligen funktionellt acceptabla mätt med validerade instrument. **Återgång till arbete**: Sju av tio patienter återgick till arbete eller motsvarande sysselsättning i två fallserier.

Risker och komplikationer: Inga dödsfall rapporterades. Förlust av transplantatet studerades i fyra fallserier med uppföljningstider 6 månader till 12 år. I ett (6 %) av 16 fall rapporterade i tre fallserier förekom förlust av transplantat på grund av avstötningsreaktion inom ett år efter transplantation. I en kinesisk fallserie rapporterades förlust av transplantatet, relaterat till bristande följsamhet till immunosuppressiv behandling i sju (64 %) av 11 fall. Övriga komplikationer rapporterades i fyra fallserier (n=27). Allvarliga sidoeffekter var vanliga med frekventa infektiösa komplikationer. Samtliga transplanterade hade minst en avstötningsepisod. Övergående hyperglykemi och vaskulära komplikationer var vanliga. Liksom vid andra organtransplantationer kan sena komplikationer relaterade till den immunosuppressiva behandlingen i form av exempelvis ökad risk för maligniteter förväntas.

***Sammanfattande kommentar*:** Hand/armtransplantation hos vuxna efter amputation förbättrar troligen ADL, och leder troligen till en användbar handmotorik och -sensorik (måttligt starkt vetenskapligt underlag, GRADE ⊕⊕⊕◯) och kan även förbättra HRQoL och förmåga att återgå till arbete (begränsat vetenskapligt underlag, GRADE ⊕⊕◯◯). Allvarliga komplikationer främst relaterade till immunosuppressionen är vanliga och behöver beaktas och diskuteras med patienten innan transplantation beslutas. Det behövs fler och större studier med långtidsuppföljning.

The above summaries were written by representatives from the HTA-centrum. The HTA-report was approved by the Regional board for quality assurance of activity-based HTA. The abstract is a concise summary of the results of the systematic review. The Swedish summary is a brief summary of the systematic review intended for decision makers, and is ended with a concluding summary.

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Head of HTA-centrum of Region Västra Götaland, Sweden, 2016-09-07

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3. Summary of Findings

Table 1

Outcomes	Number of studies Study design N = patients (hands)	Relative effect (95%CI)	Absolute effect	Certainty of evidence GRADE*
Health-related quality of life	2 Case series n=10 (16)†	> 2-fold improvement (Based on before-after data)	Not applicable	⊕⊕◯◯ Low [1, 2]
Activities of daily living	2 Case series n=16 (24)†	> 5-fold improvement (Based on before-after data)	Not applicable	⊕⊕⊕◯ Moderate [1, 3]
Hand motor function	4 Case series n=27 (37)†	Most patients achieved fair or good function in validated tests	Not applicable	⊕⊕⊕◯ Moderate [1, 3]
Hand sensory function	3 Case series n=22 (31)†	Most patients achieved fair or good function in validated tests	Not applicable	⊕⊕⊕◯ Moderate [1, 3]
Return to work	2 Case series n=10 (16)†	See absolute effect	7/10 (70 %) returned to work or similar activities	⊕⊕◯◯ Low [1, 2]
Graft loss	3 Case series n=27 (37)†	Not applicable	One reported graft loss (with adequate immunosuppression)	⊕◯◯◯ Very low [4]

Footnotes: † n= number of patients (number of hands within parentheses).

[1] Some study limitations (co-interventions not clearly described, different levels of amputations, retrospective, different follow-up periods). Uncertain precision (few cases, but clear effect compared with no transplantation).

[2] Upgraded for large magnitude of effect and obvious clinical effect.

[3] Upgraded for very large magnitude of effect and obvious clinical effect.

[4] Serious study limitations (co-interventions not clearly described, different follow-up periods). Serious imprecision (very few cases, with adequate immunosuppression).

* Certainty of evidence

High certainty ⊕⊕⊕⊕	We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty ⊕⊕⊕◯	We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty ⊕⊕◯◯	Confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.
Very low certainty ⊕◯◯◯	We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

4. Abbreviations/Acronyms

ADL	Activities of daily living
DASH	Disabilities of Arm, Shoulder and Hand
CMV	Cytomegalovirus
HRQoL	Health-related quality of life
HTSS	Hand Transplantation Scoring System
IRHCTT	International Registry of Hand and Composite Tissue Transplantation
SF-36	Short Form 36 (RAND-36)
SWMF	Semmes-Weinstein Monofilaments testing
SWLS	Satisfaction With Life Scale
SSGE	Self Subjective Global Evaluation
TAM	Total Active Motion
QoL	Quality of life
2PD	Two point discrimination

5. Background

Upper extremity amputation

Traumatic or medical upper extremity amputation represents a devastating event that can tremendously affect the life of a person both functionally and psychologically. Such consequences depend in large extent by the level of amputation and if the amputation affects one or both arms. In the first case the patient can partly adjust his/her life with the help of the contralateral healthy arm (Biddiss and Chau, 2007; Fraser, 1998), in the latter situation a personal assistant is required since manydaily life activities such as personal hygiene, dressing and cooking are impossible . Amputations proximal to the elbow joint impair even further functionality since the stump can hardly be used as a proper support in bimanual activities. In quadriamputee patients wearing the lower limb prostheses without assistance is a major problem, resulting in constant dependence on help from others.

It is unclear whether amputation of one or both arms influences the life expectancy. For lower limb amputees there is some evidence that the condition might shorten their life (Lin *et al*., 2012), but this has not been shown for upper limb amputees (Naschitz *et al*., 2008; Lin *et al*., 2010).

This HTA was initiated in order to evaluate upper extremity transplantation in adults with hand/upper extremity amputation (non-malignant causes), for decision support for introduction of bilateral upper extremity transplantation in Region Västra Götaland.

Prevalence and incidence of upper extremity amputation

There is no registry with data of the prevalence of upper extremity amputation in Sweden. The Swedish health care system keeps a registry on performed amputation surgeries. In the last 10 years (2005-2014) approximately 200 patients have undergone an amputation of the upper limb (upper arm to carpal region, NBQ03, NDQ00, NDQ11, NCQ09 and NCQ19, age 20-64 years). Amputations at the level of the wrist are most frequent, followed by upper arm, and forearm. There are no data on whether the surgery was performed on one or both arms (National Board of Health and Welfare database, http://www.socialstyrelsen.se/statistik/statistikdatabas

Present treatment of upper extremity amputation

In the acute and subacute phase after an upper extremity amputation, all patients are treated for wound healing and psychological support since most of them experience a period of loss of self-esteem and self-confidence, and also a fear of social rejection (Smurr *et al*., 2008).
Once the wounds are healed and the resulting scars are stable the patient is referred to a specialised team of therapists and orthopaedic surgeons to discuss the three main options of commercially available prostheses: cosmetic, body-powered, or myoelectric. Cosmetic prostheses provide a simple cosmetic structure that reproduces the shape and colour of the hand/arm without any possibility of active movement. Body powered or myoelectric prostheses allow the patient to have some kind of grip, controlled in the first case with the shoulder, and in the latter with electrodes placed in the musculature proximal to the amputation stump.

A further option, still experimental in the upper extremity, is the osseointegrated prosthesis developed by Brånemark (Tsikandylakis *et al*., 2014). Its main advantage is that it makes it much easier for the patients to put on and remove the prosthesis by replacing the socket anchored system with an osseointegrated screw. Transplantation after use of osseointegrated prosthesis has not been studied. However this option is potentially feasible.
Several reports have shown that 20 – 30% of upper extremity amputees abandon the use of an upper limb prosthesis, regardless of the type of device used (Tsikandylakis *et al*., 2014, Biddiss and Chau, 2007a; 2007b). The major complaints described by the patients are related to heaviness, lack of sensibility, problems related to the socket (partly solved by Brånemark) and hyperhidrosis of the stump.

The normal pathway through the health care system and current wait time for medical assessment

Patients who have suffered from either uni- or bilateral upper limb amputation are referred to the prosthesis centre. A team of specialists such as orthopaedic surgeons and therapists evaluates the amputated stump, discusses the need of the patient and provides the requested prosthesis, adjusted or changed according to different needs. Patients are called in within three months from the referral letter.

Number of patients per year who undergo current treatment regimen

Excluding amputations of fingers, and thumb, there are approximately four to five traumatic upper limb amputations yearly in the Region Västra Götaland. All patients are referred to the prosthesis centre for further discussion regarding prosthesis treatment or not. Seventy to eighty per cent of these patients will benefit from prosthesis treatment. Some of those unable to cope with a normal prosthesis might benefit from the osseointegrated device developed by Brånemark (Tsikandylakis *et al*., 2014).

Presents recommendations from medical societies or health authorities

There are no national guidelines in Sweden regarding the recommended treatment for upper limb amputees. The commonly chosen treatment option in Swedish healthcare is prosthesis replacement using one of the types mentioned earlier. For those unable to use a prosthesis there are currently no other available treatment options. The only remaining alternative is to adapt to the amputated stumps.

Hand transplantation is considered a treatment method in several countries such as USA, France and Poland, and several health care centres consider it a valuable option particularly for bilateral and quadriamputees. Hand transplantation may be considered after a period of at least six months of failed attempts to use prostheses.

6. Health Technology at issue - Hand transplantation

Hand transplantation is developed for patients who have suffered from a uni- or bilateral upper extremity amputation. The transplantation can be performed at different levels. It is assumed that the more distal transplantations have a better functional outcome.
Hand transplantation is a reconstructive procedure that can restore aesthetics and some degree of function after amputation. The first successful clinical case was performed in Lyon, France, in 1998. Since then 107 patients around the world have undergone either uni- or bilateral hand transplantations. The procedure includes harvesting the arm of a cadaveric donor for transfer to the recipient patient. As for solid organ transplantation, hand transplantation patients will need lifelong immunosuppression treatment. However there is a main difference, the transplanted hand is an organ that contains structures of different types such as skin, bone, muscle and tendons (Hautz *et al*., 2011). Among these tissues, the skin seems to be the most immunogenic component towards which the immune system reacts the most (Schneeberger *et al*., 2009).

7. Objective

The focused question

In adults with hand/upper extremity amputation (for non-malignant causes) unable to use prosthesis, does upper extremity transplantation improve long-term health-related quality of life or activities of daily living, as compared with no hand/upper extremity transplantation?

PICO: P= Patients, I= Intervention, C= Comparison, O=Outcome

P Adult patients with hand/upper extremity amputation (non-malignant causes) unable to use prosthesis (e.g. complaints about heaviness of the prosthesis, limited functionality and mobility, lack of sensation).

I Upper extremity transplantation (considering unilateral transplantations equally representative regarding the outcomes hand function, HRQoL and complications)

C No upper extremity transplantation

O <u>Critical for decision making</u>
Health-related quality of life
ADL/autonomy

<u>Important for decision making</u>
Hand function (validated instruments, e.g. HTSS, DASH)
Return to work, work ability

<u>Not important for decision making</u>
-

<u>Risks, complications</u>
Mortality
Graft loss
Other complications

8. Methods

Systematic literature search (Appendix 1)

During April 2016 two librarians (author TS and Kirsten Freadrich) performed systematic searches in Medline, Embase, the Cochrane Library, Cinahl, AMED, PsycInfo and a number of HTA-databases. Reference lists of relevant articles were scrutinised for additional references. Search strategies, eligibility criteria and a graphic presentation of the selection process are presented in Appendix 1. Two authors (PS, TS) independently of one another assessed the obtained abstracts and made a first selection of full-text articles for inclusion or exclusion. Any disagreements were resolved in consensus. The remaining articles were sent to all the authors, who read the articles independently of one another and finally decided in a consensus meeting which articles should be included in the assessment.

Critical appraisal and certainty of evidence

The included studies, their design and patient characteristics are presented in Appendix 2. The excluded studies and the reasons for exclusion are listed in Appendix 3. The included studies were critically appraised using a checklist for assessment of case series, modified from Guo *et al*, (2013) by HTA-centrum. The results and the assessed quality of each article were tabulated per outcome in Appendix 4. A summary-of-findings and the associated certainty of evidence for each outcome is presented in Table 1 (page 7). The certainty of evidence was defined according to the GRADE system (Atkins *et al.*, 2004; GRADE Working group). Grading the quality of evidence for the case series started at GRADE ⊕◯◯◯. The outcomes for hand function was in this context compared with the natural course in upper extremity amputated patients unable to use prostheses.

Ongoing research

A search in clinicaltrials.gov (2016-05-26) using the search terms (*hand transplant OR hand transplantation OR hand allotransplantation*) identified 84 trials. Eleven of these were potentially relevant for our question at issue. See more under 14 Future perspectives.

9. Results

Systematic literature search (Appendix 1)

The literature search identified 966 articles after removal of duplicates. After reading the abstracts 913 articles were excluded. Another 26 articles were excluded after reading in full text. The remaining 27 articles were sent to all authors, of which six articles (all case series) were finally included in the assessment and critically appraised. In addition, five systematic reviews and one health economy study were commented upon (Table 2).

Six case series met the inclusion criteria (Appendix 2). All the included case series had some or serious study limitations, related to poorly described co-interventions, different amputation levels, retrospective analyses, or different follow-up periods. Although precision was hampered by the scarcity of cases, a clear effect was found compared with no transplantation or the natural course after amputation. No statistical inferences comparing pre- and post-transplantation outcomes were attempted in any of the included case series.

Two of the included case series reported bilaterally transplanted patients, and in four case series both uni- and bilaterally transplanted cases were reported. For the studied outcomes: hand function, HRQoL and complications, but not for the outcomes: daily living (ADL) and return to work, the results were considered equally representative for both uni- and bilaterally transplanted individuals.

Table 2. Systematic reviews and health economy studies commented in the HTA

Author, year, country	Study design	Publication period, identified study designs	Total number of patients	Main outcome measure(-s)	Comments
Bonastre, 2012, Spain	SR	1999-2011, case reports	28	Acute rejection episodes	A total of 68 acute rejection episodes were reported in a total of 28 recipients. Publication bias?
Brugger, 2015, Switzerland	SR (HTA/ Economy)	Before Oct 2011, case reports	31	Function HRQoL Graft loss	Hand transplantation was concluded to be a controversial method, with the main problem related to be the lifelong immunosuppression due to high human, medical and economical cost in relation to the presumably marginal patient benefit.
Chung, 2010, USA	Health economy	Survey	None	Quality adjusted life years	A trade-off survey on 100 medical students. The incremental cost-utility of bilateral (but not for unilateral) hand transplantation vs. prostheses was higher than the socially acceptable threshold for general adaption of the method.
Jensen, 2012, USA	SR	1998-2011, case reports	20 with QoL related data	QoL	QoL related data reporting need to be improved in hand transplantation articles.
Landin, 2012, Spain	SR	1999-2011	28	Function Ischemia Complications	The authors conclude that hand allograft recipients showed notable functional gains. Most complications were caused by immunosuppressive protocols.
Murphy, 2013, Canada	SR	2005-2013 (according to inclusions), Designs not clearly stated	33	Mixed outcomes, but mostly complications. Also face transplants are reviewed.	The authors conclude that although vascularised composite allotransplantation is an emerging field, it is not without challenges and considerable work is still required before widespread adoption of the techniques.

Results per outcome

Unless otherwise stated, only postoperative (post-transplantation) values were presented in the case series below.

Outcomes critical for decision making

Health-related quality of life (Appendix 4:1)
Health-related quality of life (HRQoL) was reported in two case series, including a total of ten patients, with individual follow-up periods ranging from 4 to 13 years.
In one of the case series (n=5) from France, HRQoL was studied with **SSGE** (Self Subjective Global Evaluation (scale from 1 to 10, a normal hand being 10). Mean SSGE at follow-up was 7.7 (Bernandon *et al*., 2015). In the same study **SF-36** (range from 0; total disability, to 100; no disability) had a mean of 67 points for the physical component score and 65 points for the mental component score. For comparison: in a representative panel of the French population the SF-36 physical functioning had mean score of 86.5 (SD 19.7), and mental health a mean score of 67.8 (SD 19.7) (Leplège et al., 1998).
The other case series from Poland (n=5) evaluated satisfaction with life pre- and postoperatively (Chelmonski *et al*., 2015), using the **SWLS** (Satisfaction with Life Scale, ranging from 1 to 35, higher points better). The mean SWLS was 10.2 preoperatively and 23 points postoperatively (where score 10 corresponds to dissatisfaction, and 23 corresponds to average satisfaction).

Conclusion: Hand transplantation may result in major improvement in HRQoL compared with no hand transplantation in patients with upper extremity amputation for non-malignant reasons (low certainty of evidence, GRADE ⊕⊕◯◯).

Activities of daily living (ADL) (Appendix 4:1)
Activities of daily living was studied in two case series with a total of 16 patients.
In a French study (n=5) the ability to perform **65 ADL** tasks was evaluated. Preoperatively the patients could easily perform a mean 38 % of the tasks, whereas postoperatively a mean 81% of the tasks were easily completed (Bernandon *et al*., 2015). Preoperatively the same patients failed to perform 22% of the tasks, whereas postoperatively (at the final evaluation) the failure rate was 2%. The patients were also evaluated with the **400-point test** which evaluates mobility, force, single hand prehension, moving objects, and bimanual activities. The best results were achieved with the bimanual function subscale with a mean score of 74%, measured only postoperatively.
In another case series from China (n=11) at one-year follow-up, it was reported that most recipients were able to perform many functional activities (Pei *et al*., 2012). The activities were not further specified.

Conclusion: Hand transplantation, especially bilateral, probably results in major improvement in activities of daily living compared with no hand transplantation in patients with upper extremity amputation for non-malignant reasons (moderate certainty of evidence, GRADE ⊕⊕⊕◯)

Outcomes important for decision making

Hand motor function, measured with validated instruments (Appendix 4:2)
Hand motor function was studied in four case series, with a total of 27 patients, using either (or combined) the DASH (Disability Arm Shoulder Hand), HTSS (Hand Transplantation Score System), Grip strength, Carrol test, or TAM (Total Active Motion testing).

In the context of bilateral hand transplantation in patients who cannot use prostheses, hand function without transplantation is absent and all regained hand function equals improvement.

DASH score, was used in two of the included case series (Bernandon *et al*., 2015; Chelmonski *et al*., 2015). DASH is a 30-item self-reported questionnaire developed to measure physical function and symptoms (scores from 0 to 100 with lower scores indicating better function and/or improved symptoms). The normative functional DASH value from the general American population is 10. In a French case series (n=5) the mean DASH score was 15 at follow-up (4-13 years). Although not stated, this is probably the change in DASH scores from pre- to postoperatively among the French patients, i.e. the delta value of improvement (Bernandon *et al*., 2015). In a Polish case series (n=5) the mean DASH score was 67.2, but no preoperative scores were reported (Chelmonski *et al*., 2015).

The same two case series also reported hand motor function using the **HTSS** which is a score system from 0 to 100 but some items are specifically designed to test hand transplanted patients and, in contrast with the DASH, good outcomes are expressed by higher scores.
Postoperatively, at follow-up (4-8 years), the Polish study (n=5) reported mean HTSS of 76 (Chelmonski *et al*., 2015), whereas the French study (n=5) reported 'global improvement over the first 3 years', without numerical data (Bernandon *et al*., 2015).

In the French study the **grip strength** ranged from 2-16 kg, which compares to 4-28% of the age and gender norms (Bernandon *et al*., 2015).

The **Carroll** test was used in three case series (Bernandon *et al*., 2015; Kaufman *et al*., 2011; Pei *et al*., 2012) to evaluate upper extremity function in terms of pinch, grasp, grip, elbow flexion and extension, forearm pronation and supination. The test has 33 scored tasks that have a range between 0-99. Functional outcome is considered excellent for Carroll test score of 85 or higher, good for scores between 75-84, fair for scores between 51-74, and poor for scores less than 51.
The French patients (n=5) had postoperatively a mean score of 68 in the dominant hand and 53 in the non-dominant hand (Bernandon *et al*., 2015). In a series of patients from USA (n=3) the postoperative mean Carroll score was 62 (Kaufman *et al*., 2011), whereas in the Chinese material (n=11) the postoperative mean score was 68 (Pei *et al*., 2012).

Total active motion (TAM) describes the percentage of normal range of motion in the fingers. This was reported with a mean of 65% for the dominant hand and 56% for the non-dominant hand in the French group (n=5) (Bernandon *et al*., 2015), and in the Polish group the mean value was 60% (Chelmonski *et al*., 2015). The French group also reported the **wrist range of motion**, with mean flexion/extension of 32/53 degrees, and mean pronation/supination was 50/63 degrees (Bernandon *et al*., 2015).

Conclusion: Hand transplantation probably results in useful hand motor function in patients with upper extremity amputation for non-malignant reasons (moderate certainty of evidence, GRADE ⊕⊕⊕◯).

Hand sensory function (Appendix 4:3)
Hand sensory function was reported in three case series with a total of 22 patients (Bernandon *et al*., 2015; Kaufman *et al*., 2011; Pei *et al*., 2012), by using either (or combined) the two-point discrimination test (2pd) (including protective sensation), the Semmes-Weinstein Monofilament Test (SWMF), and the Modified Highet scale (including cold/hot sensation).

Two-point discrimination test was used in three case series (Bernandon *et al*., 2015; Kaufman *et al*., 2011; Pei *et al*., 2012). It evaluates the smallest distance perceived by the patient when two points are applied on the fingertips. Normal values are considered to be below 6 mm. Protective sensation considered at or above 11 mm.

In a French case series, all patients (n=5) regained static 2pd between 6-15 mm (Bernandon *et al*., 2015), as also did the only patient reported in Kaufman *et al*., 2011). In a Chinese case series 2pd between 1.5-6 mm (n=11) was found (Pei *et al*., 2012), although 1.5 mm is difficult to detect even in a normal population.
All the French and Chinese patients regained protective sensation (Bernandon *et al*., 2015; Pei *et al*., 2012). Four of six patients from USA regained protective sensation (no data on two patients due to graft loss or short follow-up) (Kaufman *et al*., 2011).

The **SWMF** test, with a kit of monofilaments with different thickness that are applied on the skin until they bend, was used in one case series (Bernandon *et al*., 2015). In SWMF test the patient should indicate which filament he/she is able to feel on the skin. The thicker the filament, the stronger the force applied on it, indicating less sensation. Sizes between 1.65 and 2.83 mm indicate normal sensation, and between 3.22 and 3.61 indicate diminished light touch. All the French patients (n=5) could detect filaments between 3.61-2.83 (Bernandon *et al*., 2015).

The **modified Highet scale**, used in one case series (Bernandon *et al*., 2015), is categorised from S0 (no sensation) to S4 (complete recovery). The French patients had a mean of S3+, indicating return of superficial cutaneous pain and tactile sensibility without over response (Bernandon *et al*., 2015). All patients in the French case series and four patients out of six in the group from USA regained hot/cold sensation (missing data on two) (Bernandon *et al*., 2015; Kaufman *et al*., 2011).

Conclusion: Hand transplantation probably results in protective-, temperature- and tactile hand sensory function in patients with upper extremity amputation for non-malignant reasons (moderate certainty of evidence, GRADE ⊕⊕⊕◯).

Return to work (Appendix 4:1)
Return to work was reported in two case series with a total of ten patients (Bernandon *et al*., 2015; Chelmonski *et al*., 2015). Six out of ten patients returned to work and one became active in non-profit organisations.

Conclusion: Hand transplantation, especially bilateral, may improve the frequency of return to work compared with no hand transplantation in patients with upper extremity amputation for non-malignant reasons (low certainty of evidence, GRADE ⊕⊕◯◯).

Work ability
The outcome was not studied.

Risks, complications (Appendix 4:4)
Regarding the outcome **mortality**, no fatalities were reported. **Graft loss** was studied in four case series with follow-up periods ranging from six months to 12 years (Kaminska *et al*., 2014; Kaufman *et al*., 2011; Pei *et al*., 2012; Petruzzo *et al*., 2015). In one (6%) of 16 western world cases, a rejection resulting in graft loss occurred within the first year after transplantation. In China, graft loss was reported in seven (64%) of 11 cases related to poor compliance to immunosuppressive treatment. **Other complications** were reported in four case series including a total of 27 patients. Serious complications were common with frequent infectious complications (48%), including reactivation of latent viral infections and opportunistic bacterial infections. All recipients had at least one acute rejection episode. Transient hyperglycaemia (some of these patients may develop insulin dependency, Boratynska *et al*., 2014) was common, as were vascular complications. As for all organ transplantations, late adverse effects such as malignancies and high blood pressure related to immunosuppression are to be expected.

10. Ethical issues

In contrast to solid organ transplantation hand transplantation is not a lifesaving procedure but a procedure with the potential to improve quality of life. This requires in-depth risk/benefit analysis as well as informed full understanding of these analyses by the patient.
Cost-effectiveness is difficult to estimate but is considered to be in favour of prosthetic replacement compared with transplantation. Since hand transplantation is only performed in highly selected cases and the number of patients is very small the cost for the treatment may probably be considered sustainable.
Hand transplantation as a treatment requires no new legislation. The hand is defined as an organ and hand transplantation is possible within existing regulations (Socialstyrelsen, 2016). Current laws and regulations for organ donation apply for hand transplantation. However, because it is a new treatment modality one cannot automatically assume that the stated will for someone to donate organs (stated in the donation registry) includes the upper extremities.
From an ethical point of view, it could be argued that once the patient is thoroughly informed of the potential complications following hand transplantation, he or she should have the right to choose a treatment that can improve the quality of life. See also Appendix 5.

11. Organisational aspects

Time frame for the putative introduction of hand transplantation

Hand transplantation can be realised thanks to the collaboration of several departments, primarily hand surgery, transplantation and physiotherapy. The surgical procedure as well as the medical treatments are already well established at Sahlgrenska University Hospital. The hand surgery department routinely performs autologous replantation surgery in the acute setting. Hand transplantation is similar to hand replantation, with the advantage that every step is thoroughly planned ahead depending on the level of the initial injury.

The immunosuppressive therapy is similar to the protocols used in solid organ transplantation. The department of transplantation at Sahlgrenska University Hospital is the largest transplantation centre in Sweden performing a large number of organ transplants every year (371 in 2015) and is a national centre for heart, lung, and multi-organ transplantation. Compared with solid organ transplantation, acute rejection is more easily diagnosed being evident on the skin. This allows early action against rejection.

Furthermore, the physiotherapy department has extensive experience in rehabilitation of replanted upper extremities which, as mentioned above, does not differ from transplanted upper extremities. The patient will undergo intensive training in the hospital during the first postoperative month. Later on the patient will visit the district physiotherapist for further training instructions.

The hand surgery department leads and coordinates a team of specialists which includes, e.g., pathologists, dermatologists, and a psychologist.

Present practise of hand transplantation in other hospitals

The hand surgery society in Sweden has decided to start a hand transplant program for patients who have undergone bilateral upper extremity amputation and who cannot cope with the use of any prosthesis. Göteborg and Stockholm are exploring the possibility to become a referral centre to perform the surgical procedure. The other hand surgery departments in Sweden will cooperate regarding the postoperative rehabilitation and follow ups.

Consequences for personnel of introduction of hand transplantations

The procedure involves coordinators, operating nurses, and personnel working with transplantation and hand surgery. Because of the large amount of clinical and surgical activities already performed in these departments there is no need for new infrastructures and, due to the very few possible hand transplantations annually, we do not expect any major interference with the regular activity. Physiotherapy will need to be intense in the first several weeks and one or two physiotherapists will be dedicated to the patient between two and four hours per day.

Consequences for other clinics or supporting functions at the hospital or in the Region Västra Götaland

The surgical procedure will be performed by four surgeons (two surgeons per arm). From the time the team is informed of a potential donor, to the actual transplantation about twelve hours of preparation are necessary. In case the involved surgeons have elective surgeries or outpatient clinic, this twelve hours' time is enough to reorganise their other duties properly. As mentioned above, teams from other centres and particularly Stockholm and Malmö are willing to offer their assistance in case of need. Again, we do not expect a major impact on the regular activity neither in our centre nor in other centres in the Region.

12. Economic aspects

Approximately four to five upper limp amputations are performed annually in the Region Västra Götaland. According to previous reports (Tsikandylakis *et al*., 2014, Biddes and Chau, 2007a; 2007b), 20 – 30 per cent of upper extremity amputees will not benefit from an upper limb prosthesis and are thereby in need of another alternative. Thus, the calculation of the economic aspects is based on one possible patient per year.

Expected costs of no upper extremity transplantation

Due to reduced ADL function, bilateral hand amputated patients are in need of daily personal assistance for approximately eight hours per day. Försäkringskassan provides an allowance of 288 SEK per assistance hour, hence the annual total cost of personal assistance per patient is estimated to 840,960 SEK. In addition, unpaid caregivers as family members and friends are most likely to provide extensive support, but this support is not included as a cost in this economic analysis.

Expected costs of bilateral hand transplantation

Cost for health care of bilateral hand transplantation

The estimated cost of unilateral hand transplantation is based on the replantation of an upper limb at the Sahlgrenska University hospital during 2014. The cost for the surgery and the inpatient care after the surgery (approximately five days) was 260,000 SEK. The outpatient care after the surgery during the following year was 42,000kr, which consisted of follow-up visits with physicians and occupational therapists. The estimated cost of bilateral hand transplantation includes more surgeons (at least four, two per limb), nurses and potentially longer time in the operation theatre. The teams are working parallel with both hands and hence the excess time of bilateral hand transplantation is estimated to be 1.5 times the unilateral hand transplantation and hence equal to 390,000 SEK. If we add the cost per year for the outpatient visits we have a total cost of 432,000 SEK only for the transplantation without including immunosuppression.

Compared to replantation of an upper limb, the patient after a hand transplantation will stay in the intensive care unit for a total of two days, and have a longer initial inpatient care after surgery, in total about 10 days. Preoperatively several blood test and x-rays, angiography, CT-scan and MRI are performed. Approximately this cost is estimated in approximately 100,000 SEK.

Cost for immunosuppression during the first year of treatment

For induction therapy, either Simulect or Thymoglobulin are used. Simulect is given two times (20mg) per year with a total annual cost of 24,486 SEK. Thymoglobulin is given 20 times (6mg/kg) the first year, with an annual cost of 42,980 SEK. For maintenance therapy, Tacrolimus and Mycophanolate mofetil are used. Tacrolimus is given 2,190 times (3mg) the first year with an annual cost of 37,230 SEK. Mycophanolate mofetil is given 1460 times (1g) the first year with an annual cost of 11,504 SEK. For cortison treatment, Prednisolone is given 730 times (10mg) the first year with an annual cost of 840 SEK. For antiviral medication, Valcyte is given 90 times (450mg) the first three months with a total cost of 22,153 SEK. In addition, blood test to adjust the medication doses according to blood levels is ordered for approximately 10 times during the year with a total annual cost of 8,000 SEK. The total cost during the first year after a hand transplantation for immunosuppression is 104,213 SEK when Simulect is used, and 122,707 SEK when Thymoglobulin is used.

Cost for immunosuppression after the first year of treatment

For maintenance therapy, Tacrolimus and Mycophanolate mofetil are used. Tacrolimus is given 2,190 times (2mg) per year with an annual cost of 24,82 0SEK. Mycophanolate mofetil is given 1460 times (1g) per year with an annual cost of 11,504 SEK. For cortison treatment, Prednisolone is given 365 times (5mg) per year with an annual cost of 420 SEK. In addition, blood test to adjust the medication doses according to blood levels is ordered for approximately two times per year with a total annual cost of 1,600 SEK. The total annual cost after the first year is 38,344 SEK.

Expected total costs of bilateral hand transplantation

The total cost during the first year is estimated to 636,231 SEK (654,707 SEK when Thymoglobulin is used). The total cost after the first year is estimated to 38,344 SEK for immunosuppression.

Additional cost for complications might include readmission for rejection (which most likely occurs at least once during the first year post-transplantation), vascular complications, infections, and possible secondary surgical procedures such as tenolysis (similar to replantation). We have estimated this cost to be in a range between 10.000 and 40.000 SEK and depends on whether and how many interventions the patient undergo after surgery. However we have not included the cost for medical treatment in case of new onset diabetes or high blood pressure which is reported to occur in patients under immunosuppression. The cost of organ procurement is not included since this is a shared cost between many specialties due to multiple organ retrieval.

Total change of cost

The medical cost for a patient with no upper extremity transplantation is negligible, however due to reduced ADL function this patient needs full support every day from paid and unpaid carers. With a bilateral hand transplantation and hence improved ADL function, the support from personal assistance and relatives will probably be needed to a much lower extent. This reduction in cost for the society will compensate the cost for the bilateral hand transplantation. If the patient is able to return to work after surgery the cost is highly compensated.

Possibility to adopt and use the new technology within the present budget

Although part of the cost is similar to replantation, as shown above, a transplantation of an upper extremity is more expensive regarding medication, clinical follow-ups, and resources for surgery that presently are not included in our budget.

Available economic evaluations or cost advantages/disadvantages

A cost analysis by Brügger *et al*, (2015), has been performed in the Swiss setting analysing life-long costs for hand transplantation in comparison with prosthesis for a 35-year-old unilaterally amputated base case patient. The life-long costs for the hand transplantation was estimated to EUR 810,500 and for the prosthesis EUR 524,300, including direct medical costs and indirect costs as reduced earnings capacity. The difference in direct medical costs was estimated to EUR 438,500, of which 40% was due to the cost for immunosuppression. However, due to the lower invalidity of the transplanted patient, the indirect cost was estimated to be lower by EUR 152,300. A sensitivity analysis was conducted, varying the discount rate and life expectancy, whereof the discount rate had a significant effect due a large share of the cost was caused by immunosuppression in the future.

A cost-utility analysis by Chung et al, 2010, has been performed in the American setting, also comparing uni- and bilateral hand transplantation with prosthesis, modelled for a male with remaining life-years of 40 years. The incremental cost-effectiveness ratio was $381,961/QALY, and hence not considered a cost-effective alternative with the traditionally accepted of $50,000/QALY. The utility was measured with the time-trade-off (TTO) for uni- and bilateral hand transplantations in a survey of 100 (non-amputated) medical students which was used to estimate the QALYs during the 40 years in the model. The validity of using proxy reports, i.e. information is collected on behalf of the patients, is problematic to determine which also has been discussed by Concannon (2009).

13. Discussion

Summary of main results

The present literature search identified only six case series with at least five patients, describing three unique patient groups from different perspectives.
Based on low certainty of evidence, hand transplantation may improve health-related quality of life, and based on moderate certainty of evidence it probably improves activity of daily life, as well as it restores some degree of hand motor and sensory function.

It should be noticed that especially from the psychological evaluation of the patients, functionality, always expressed by numbers, does not necessarily give justice to that state of well-being that the patients express by personal interviews with the psychologist as described by the Polish group. This represents a considerable improvement after transplantation, since the patient regains confidence, feels social approval and a sense of completeness, with restoration of the body form previously lost.
Transplanting a hand is in all similar to transplanting a solid organ and, as such, similar types of complications deriving from the immunosuppression treatment must be expected. These are related to infections, metabolic complications such as diabetes, cardiovascular complications as well as tumours. The risk of such future events must be well explained to and understood by patients whose main wish is improved quality of life.
As in autologous replantation, further surgical procedures including tenolysis, joint fusion, or tendon transfers might be necessary during follow up to improve function. These cannot be predicted and it is related to the relative gain in mobility and dexterity of the grafted hand.

Overall completeness and applicability of evidence

Although we have few cases of long-term follow up with more than 10 years survival, we lack systematic reviews of larger case series.

Agreements and disagreements with other studies and reviews

There seems to be a general agreement on the benefit of hand transplantation regarding improvement in quality of life and functionality assessed by both DASH score and HTSS particularly in bilateral cases (Chelmonski *et al*., 2015; Bernardon *et al*., 2015; Kauffman *et al*., 2011).
Two articles have compared hand transplantation to upper extremity prosthesis (Chung et al., 2009; Brügger *et al*., 2015). We disagree on the methodology and the results since candidates for hand transplantation are only those patients who, after an attempt of at least six months, cannot use prosthesis to replace their missing hand(s). Hand transplantation should never be offered as an alternative to a functioning prosthesis, as the previously mentioned comparison might imply. Even though it is of great interest to understand the differences in costs and the potential complications of these two types of treatments, it is important to highlight that in the here addressed context hand transplantation can only be compared with amputated stumps since these are the only patients that we intend to enrol in a transplantation program.
Even if a comparison between transplantation and prosthesis users is done in literature reviews, the article from Switzerland (Brügger *et al*, 2015) fails to compare and properly assess these two groups. In this article for instance the DASH score reached by patients reported in the IRCHTT (2010) after only one year of bilateral transplantation is compared with long-term prosthesis users, the majority being unilateral amputees. Thus the authors compare two totally different groups of patients: one large group of unilateral amputees with long-term prosthetic use is compared with a group of bilateral amputees after only one year follow up. Based on this unbalanced comparison, the authors conclude that prosthesis users show better functional results.

14. Future perspective

Scientific knowledge gaps

Presently one of the main problems is the lack of a systematic evaluations and different methods for assessment of the patients pre- and postoperatively, making comparisons difficult.

Ongoing research

A search in Clinicaltrials.gov (2016-05-26) identified 84 trials, 11 of which were potentially relevant for our question at issue:

NCT02165865: Single group study on traumatic amputation of arm or hand. Status: Recruiting
NCT01565187: Development of a psychosocial assessment database related to hand transplantations. Status: Enrolling by invitation
NCT00778856: Single group study on hand transplantation for the reconstruction of below the elbow amputations. Status: Terminated
NCT01618682: Observational case only, studying cortical organisation in allogeneic transplants or heterotopic hand replants. Status: Recruiting
NCT02310867: Single group study on immunosuppression in hand transplants. Status: Recruiting
NCT00722280: Single group study on hand transplantations. Status: Enrolling by invitation
NCT01459107: Single group study on human upper extremity allotransplantation. Status: Recruiting
NCT02331355: Observational study (cases only) on hand transplantation. Status: Not yet recruiting
NCT02476838: Single group study on hand transplantation. Status: Not yet recruiting
NCT01293214: Single group study on vascularised composite allotransplantation for multiple extremity amputations. Status: Recruiting
NCT00711373: Single group study on vascularised composite allotransplantation of the hand. Status: Recruiting

Implications for research

The possibility of introducing hand transplantation in Gothenburg would allow us to compare functionality, quality of life, costs and complications of different groups of patients enrolled in different types of treatments such as myoelectric prosthesis, osseointegrated prosthesis and transplantation. No such study has yet been published.

Even though a relatively low number of cases are expected in the next few years in Sweden, these cases will give a significant contribution to the patients and to this field not only in Sweden, but in the whole community of composite allotransplantation.

As for organ transplantation, there is a large amount of ongoing research regarding the possibility to reduce rejection and improve long-term survival and function of the grafted hand.
Our group has obtained ethical approval to study cortical reorganisation by means of functional MRI after transplantation. Cortical reorganisation happens in a part of a brain with decreased sensory input following amputation and adjacent brain areas that still receive input takes over.

15. Participants in the project

The question was nominated by

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Participating health care professionals

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Declaration of interest

None

Project time

HTA was accomplished during the period of 2016-03-24 – 2016-09-07.
Literature searches were made in April 2016

Appendix 1, Search strategy, study selection and references

PICO

Question at issue:
In adults with hand/upper extremity amputation (for non-malignant causes) unable to use prosthesis, does upper extremity transplantation improve long-term health-related quality of life or activities of daily living, as compared with no hand/upper extremity transplantation?

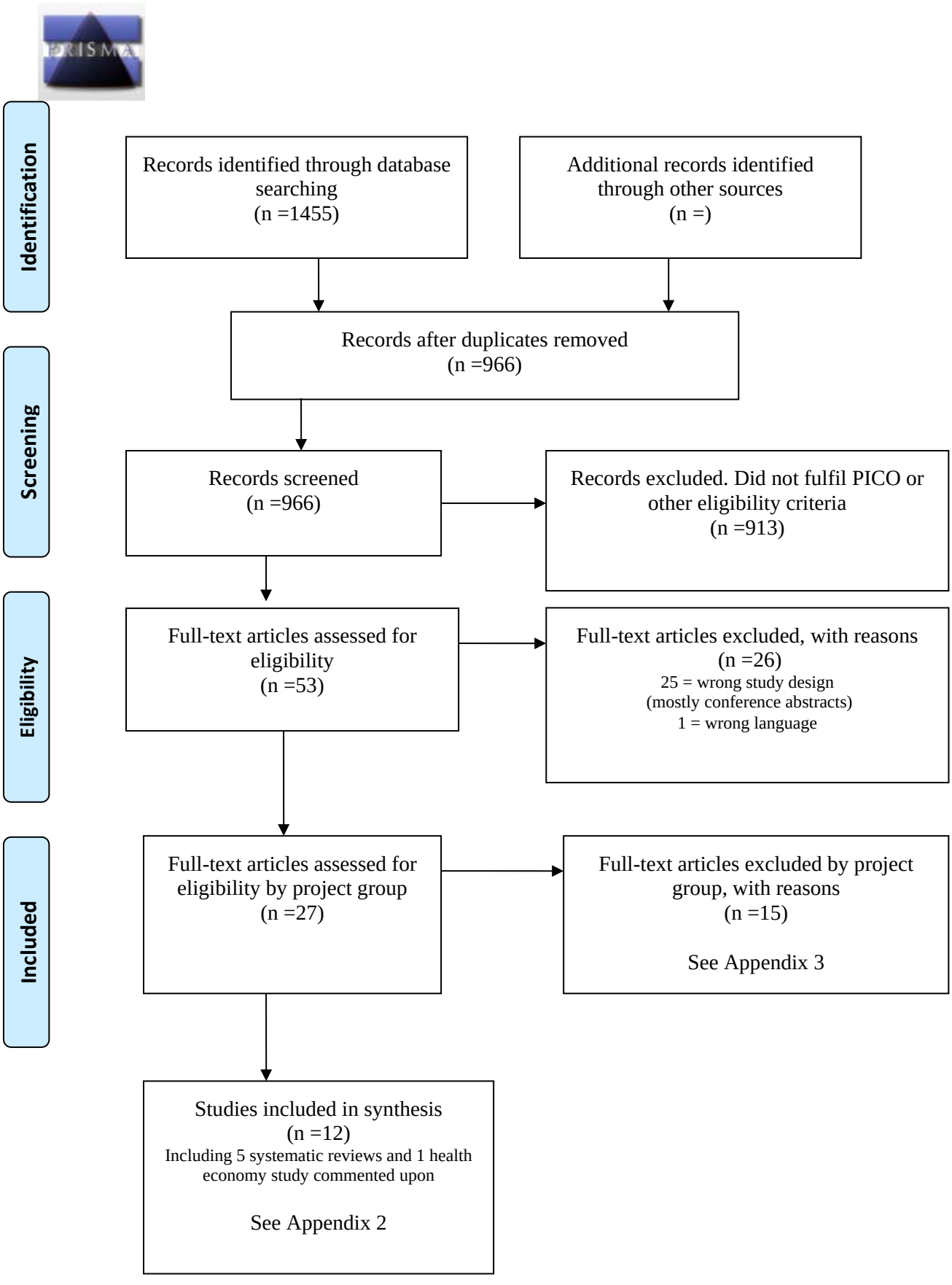
P	Adult patients with hand/upper extremity amputation (non-malignant causes) unable to use prosthesis (e.g. complaints about heaviness of the prosthesis, limited functionality and mobility, lack of sensation).
I	Upper extremity transplantation (considering unilateral transplantations equally representative regarding the outcomes hand function, HRQoL and complications)
C	No upper extremity transplantation
O	<u>Critical for decision making</u> Health-related quality of life ADL/autonomy <u>Important for decision making</u> Hand function (validated instruments, e.g. HTSS, DASH) Return to work, work ability <u>Not important for decision making</u> - <u>Risks, complications</u> Mortality Graft loss Other complications

Study design:
Systematic reviews
Randomised controlled trials
Non-randomised controlled studies
Case reports/case series ≥ 5 patients

Publication year:
1998-

Language:
English, French, German, Scandinavian languages

Selection process – flow diagram



Search strategies

Database: Medline (**Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R)** 1946 to Present
Date: 2016-04-04
No of results: 550

#	Searches	Results
1	(Hand or Arm or upper extremity or upper extremities or upper limb or upper limbs or midforearm$ or forearm$).ti.	69090
2	(Transplant$ or allotransplant$ or vasculari#ed composite or allograft$).ti.	233948
3	1 and 2	660
4	exp Hand Transplantation/	355
5	(vasculari#ed composite allotransplant$ or composite tissue transplant$ or composite tissue allograft$ or composite tissue allotransplant$).ti.	330
6	3 or 4 or 5	1032
7	(animals not (animals and humans)).sh.	4175932
8	(animal or animals or mice or mouse or rat or rats or monkey$ or primate$).ti.	1337858
9	7 or 8	4395180
10	6 not 9	902
11	(renal or kidney$ or cardiac or heart or lung or liver or stem cell$).ti.	1334491
12	10 not 11	818
13	(editorial or comment).pt.	928947
14	12 not 13	759
15	**limit 14 to (yr="1998 -Current" and (danish or english or french or german or norwegian or swedish))**	**550**

Database: PubMed
Date: 2016-04-04
No of results: 82

Search	Query	Items found
#22	**Search #12 AND #13 Filters: Publication date from 1998/01/01; Swedish; Norwegian; German; French; English; Danish**	**82**
#15	Search #12 AND #13 Filters: Publication date from 1998/01/01	82
#14	Search #12 AND #13	87
#13	Search pubmednotmedline[sb] OR inprocess[sb] OR publisher[sb]	2835237
#12	Search #7 NOT #11	823
#11	Search #8 OR #9 OR #10	3406371
#10	Search Editorial[ptyp] OR Comment[ptyp]	927293
#9	Search animal[ti] or animals[ti] or mice[ti] or mouse[ti or rat[ti] or rats[ti] or monkey*[ti] or primate*[ti]	1342877
#8	Search renal[ti] or kidney*[ti] or cardiac[ti] or heart[ti] or lung[ti] or liver[ti] or stem cell*[ti]	1345440
#7	Search #3 OR #5 OR #6	1030

#6	Search vascularised composite allotransplant*[ti] or vascularized composite allotransplant*[ti] or composite tissue transplant*[ti] or composite tissue allograft*[ti] or composite tissue allotransplant*[ti]	329
#5	Search "Hand Transplantation"[Mesh]	347
#3	Search #1 AND #2	660
#2	Search transplant*[ti] or allotransplant*[ti] or vascularised composite[ti] or vascularized composite[ti] or allograft*[ti]	234593
#1	Search hand[ti] or arm[ti] or upper extremity[ti] or upper extremities[ti] or upper limb[ti] or upper limbs[ti] or midforearm*[ti] or forearm*[ti]	69859

Database: EMBASE 1974 to 2016 April 01 (OVID SP)
Date: 2016-04-04
No of results: 661

#	Searches	Results
1	exp hand transplantation/	179
2	(Hand or Arm or upper extremity or upper extremities or upper limb or upper limbs or midforearm$ or forearm$).ti.	81623
3	(Transplant$ or allotransplant$ or vasculari#ed composite or allograft$).ti.	315085
4	2 and 3	831
5	(vasculari#ed composite allotransplant$ or composite tissue transplant$ or composite tissue allograft$ or composite tissue allotransplant$).ti.	440
6	1 or 4 or 5	1273
7	(animal not (animal and human)).sh.	1305906
8	(animal or animals or mice or mouse or rat or rats or monkey$ or primate$).ti.	1550692
9	7 or 8	2606162
10	6 not 9	1171
11	(renal or kidney$ or cardiac or heart or lung or liver or stem cell$).ti.	1704762
12	10 not 11	1032
13	**limit 12 to (embase and (danish or english or french or german or norwegian or swedish) and yr="1998 -Current")**	**661**

Database: CINAHL, AMED, PsycINFO (EBSCO)
Date: 2016-04-04
No of results: 77

#	Query	Result
S10	**S7 NOT S8** Avgränsare - Publiceringsdatum: 19980101-20161231; Språk: Danish, English, French, German, Norwegian, Swedish	**77**
S9	S7 NOT S8	81
S8	TI animal or animals or mice or mouse or rat or rats or monkey* or primate	156,250
S7	S5 NOT S6	82
S6	TI renal or kidney* or cardiac or heart or lung or liver or "stem cell" or "stem cells"	133,300

S5	S3 OR S4	93
S4	S1 AND S2	84
S3	TI ("vasculari?ed composite allotransplant*" or "composite tissue transplantation" or "composite tissue allograft*" or "composite tissue allotransplant*")	9
S2	TI (Transplant* or allotransplant* or "vasculari?ed composite" or allograft*)	17,579
S1	TI (Hand or Arm or "upper extremity" or "upper extremities" or "upper limb" or "upper limbs" or midforearm* or forearm*)	27,343

Database: The Cochrane Library
Date: 2016-04-04
No of results: 85
Cochrane reviews 4
Other reviews 1
Trials 74
Technology assessments 1
Economic evaluations

ID	Search	Hits
#1	Hand or Arm or upper extremity or upper extremities or upper limb or upper limbs or midforearm* or forearm* (Word variations have been searched)	70529
#2	transplant* or allotransplant* or vascularised composite or vascularized composite or allograft* (Word variations have been searched)	26958
#3	MeSH descriptor: [Hand Transplantation] explode all trees	2
#4	#1 near/3 #2	191
#5	(vascularised composite allotransplant* or vascularized composite allotransplant* or composite tissue transplant* or composite tissue allograft* or composite tissue allotransplant*):ti	0
#6	#4 or #4 or #5	191
#7	renal or kidney* or cardiac or heart or lung or liver or stem cell or stem cells:ti (Word variations have been searched)	64830
#8	**#6 not #7**	**85**

Reference lists
A comprehensive review of reference lists brought no new records

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Reference lists

Included studies:

Case-series:

Bernardon L, Gazarian A, Petruzzo P, Packham T, Guillot M, Guigal V, et al. Bilateral hand transplantation: Functional benefits assessment in five patients with a mean follow-up of 7.6 years (range 4-13 years). J Plast Reconstr Aesthet Surg. 2015;68(9):1171-83.

Chelmonski A, Kowal K, Jablecki J. The Physical and Psychosocial Benefits of Upper-Limb Transplantation: A Case Series of 5 Polish Patients. Ann Transplant. 2015;20:639-48.

Kaminska D, Koscielska-Kasprzak K, Myszka M, Banasik M, Chelmonski A, Boratynska M, et al. Significant infections after hand transplantation in a Polish population. Transplant Proc. 2014;46(8):2887-9.

Kaufman CL, Breidenbach W. World experience after more than a decade of clinical hand transplantation: update from the Louisville hand transplant program. Hand Clin. 2011;27(4):417-21, vii-viii.

Pei G, Xiang D, Gu L, Wang G, Zhu L, Yu L, et al. A report of 15 hand allotransplantations in 12 patients and their outcomes in China. Transplantation. 2012;94(10):1052-9.

Petruzzo P, Gazarian A, Kanitakis J, Parmentier H, Guigal V, Guillot M, et al. Outcomes after bilateral hand allotransplantation: a risk/benefit ratio analysis. Ann Surg. 2015a;261(1):213-20.

Systematic reviews, no appraisal done, only commented on:

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HTA Hand transplantation
Appendix 2 – Characteristics of included studies

Author, Year, Country	**Study Design**	**Follow-up period**	**Intervention/ uni- or bilateral**	**Patients (n)**	**Age (range)**	**Men (%)**	**Outcome variables** (defined in PICO)
Bernardon, 2015, France	Case-series	4-13 yrs.	Bilateral n=5 Unilateral n=0	5	21-33 yrs.	80 %	ADL HRQoL Hand motor function (validated instruments) Hand sensory function Return to work Complications (see Petruzzo *et al*., 2015a)
Chelmonski, 2015, Poland	Case-series	4-8 yrs.	Bilateral n=1 Unilateral =4	5	29-60 yrs. (at the time of the report)	80 %	HRQoL Hand motor function (validated instruments) Hand sensory function Return to work Complications (see Kaminska *et al*., 2014)
Kaminska, 2014, Poland	Case-series	3-9 yrs.	Bilateral n=1 Unilateral n=4	5	30-50 yrs.	80 %	Complications
Kaufman, 2011, USA	Case-series	6 m-12 yrs.	Bilateral n=1 Unilateral n=5	6	32-54 yrs.	100 %	Hand motor function (validated instruments) Hand sensory function Complications
Pei, 2012, China	Case-series	16-112m	Bilateral n=3 Unilateral n=8	11	19-52 yrs.	91.6 %	ADL Hand motor function (validated instruments) Complications
Petruzzo, 2015a, USA	Case-series	3-13 yrs.	Bilateral n=5	5	21-33 yrs.	80 %	Complications

ADL = Activities of daily life, HRQoL = Health related quality of life.

Appendix 3. Excluded articles – HTA Hand transplantation

Study author, publication year	Reason for exclusion
Boratynska, 2014	Wrong outcome and duplicate regarding complications with Chelmonski, 2015
Breidenbach, 2016	Narrative review and data not extractable on own cases
Fischer, 2014	Non-systematic review
Jablecki, 2011	Case series with data on <5 patients
Jablecki, 2009	Wrong comparison (replantation)
Kaufman, 2009	Duplicate publication with Kaufman, 2011
Kaufman, 2013	Wrong P – not hand transplants specified
Lang, 2012	Wrong scope - anesthesia
Petruzzo, 2011	Duplicate publication with Petruzzo, 2015
Lanzetta, 2004	Duplicate publication with Bernandon, 2015
Petruzzo, 2015b	Congress abstract
Schneeberger, 2013	Wrong intervention
Schneeberger, 2005	Wrong scope – four selected cases with cytomegalovirus infection
Shores, 2015	Non-systematic review
Zhu, 2014	Data not extractable on individual level

Project: Hand transplantation
Appendix 4:1
Outcome variable: Health related quality of life (HRQoL) and Activities of Daily Life (ADL)

* + No or minor problems
? Some problems
- Major problems

Author, year, country	Study design	Number of patients n=	With drawals - dropouts	Activity of daily life (ADL) / Quality of life (QoL)						Comments	Directness *	Study limitations *	Precision *
				400-point test (0-100%)	Easily ability to perform 65 ADL tasks (0-100%)	Self-subjective global evaluation (SSGE) (0-10 points)	RAND-36 (SF-36)	Satisfaction with life scale (SWLS) (5-35)	Return to work				
Bernandon, 2015, France	Case-series	5 all bilateral	0	Dominant hand, mean (range): 55.8% (43-66%) Non dominant hand, mean (range): 49.4% (40-64%) Bimanual function subscale, mean (range): 74% (53-87%)	Preoperative, mean (range): 38 % (5-63%) Postoperative, mean (range): 81% (74-91%)* *Failed to perform tasks* Preoperative, mean (range): 22% (11-43%) Postoperative, mean (range): 2% (0-3%)*	Mean (range): 7.7 points (3-10 points)	Physical component summary (0-100): Mean: 67 points Mental component summary (0-100): Mean: 65.25 points	Not reported	n=2	Time of follow not always specified Increase of ability to perform ADL tasks and decrease in failed tasks pre-/ postoperative * p-values not stated	+	+/?	-
Chelmonski 2015, Poland	Case-series	5 Uni/Bi-lateral: 4/1	0	Not reported	Not reported	Not reported	Not reported	Before transplantation Mean (range): 10.2 (8-13) Median: 9 After transplantation Mean(range): 23 (18-29) Median: 24	n=4 work n=1 active in non-profit organizations	At latest time point follow up Great psychosocial benefit not only determined by the function of the grafted hand(s)	+	?	-

Project: Hand transplantation
Appendix 4:1
Outcome variable: Health related quality of life (HRQoL) and Activities of Daily Life (ADL)

* + No or minor problems
? Some problems
- Major problems

Author, year, country	Study design	Number of patients n=	With drawals - dropouts	Activity of daily life (ADL) / Quality of life (QoL)						Comments	Directness *	Study limitations *	Precision *
				400-point test (0-100%)	Easily ability to perform 65 ADL tasks (0-100%)	Self-subjective global evaluation (SSGE) (0-10 points)	RAND-36 (SF-36)	Satisfaction with life scale (SWLS) (5-35)	Return to work				
Pei 2012, China	Case-series	11 Uni/Bi-lateral: 8/3	0	Not reported	Most recipients were able to perform many functional activities† at 1-year follow-up	Not reported	Not reported	Not reported	Not reported	† Reported in the discussion section. The activities were not specified.	+	?	-

2400-point test: Motor skills, strength, bimanual coordination, 100% = best result. ADL – Activities of daily living. SSGE: 10 points = best result. SWLS: 5-17=low result, 18-32=medium result, 24-35=high result.

Project: Hand transplantation
Appendix 4.2
Outcome variable: Hand motor function

* + No or minor problems
? Some problems
- Major problems

Author, year, country	Study design	Number of patients n=	With drawals - dropouts	Hand function						Comments	Directness *	Study limitations *	Precision *
				Carroll test dominant hand (0-99 points) non dominant (0-96 points)	Grip strength (kg)	Total active motion (TAM) dig I-IV (% of normal range of motion)	Wrist motion (range - degrees)	DASH (100-0)	HTSS (0-100)				
Bernandon, 2015, France	Case-series	5 Uni/bi-lateral: 0/5	0	Dominant hand Mean (range): 68 (57-87) Non dominant Mean (range): 52.8 (37-78)	Mean (range): 10.8 (2.0-16.3) kg (i.e. 4-28% of age and gender norms)	Dominant hand Mean (range): 65.2 (37.5-91) % Non-dominant Mean (range): 55.6 (31-93) %	Flexion Mean (range): 32 (0-70)° Extension Mean (range): 53 (25-70)° Pronation Mean (range): 50 (5-80)° Supination Mean (range): 63 (-5-90)°	Mean (range): 15 (4-42)	Global improvement over the first 3 years (no values reported)	Latest time point of follow up: Mean: 7.6 (range 1-13) yrs.	+	+/?	-
Chelmonski, 2015, Poland	Case-series	5 Uni/bi-lateral: 4/1	0	Not reported	Not reported	Median: 58% Mean (range): 59.8 (45-80) %	Not reported	Median: 66 Mean (range): 67.2 (56-77)	Median: 76 Mean (range): 74 (62-89)	4-8 year postoperative follow up time. The article focuses on psychosocial results.	+	?	-

Project: Hand transplantation
Appendix 4.2
Outcome variable: Hand motor function

* + No or minor problems
? Some problems
- Major problems

Author, year, country	Study design	Number of patients n=	With drawals - dropouts	Hand function						Comments	Directness *	Study limitations *	Precision *
				Carroll test dominant hand (0-99 points) non dominant (0-96 points)	Grip strength (kg)	Total active motion (TAM) dig I-IV (% of normal range of motion)	Wrist motion (range - degrees)	DASH (100-0)	HTSS (0-100)				
Kaufman, 2011, USA	Case-series	6 Uni/bi-lateral: 5/1	3*	Mean (range): 61.7 (57-69) n=3	Not reported	Not reported	Not reported	Not reported	Not reported	4-12 year postoperative follow up time. * Data not available for 3 patients due to: graft loss (n=1), short follow-up (n=2)	+	?	-
Pei. 2012, China	Case-series	11 Uni/bi-lateral: 8/3	1*	Mean (range): 68.4 (50-86) Median: 72	Not reported	Not reported	Not reported	Not reported	Not reported	One graft amputated before evaluation 1-year postop.	+	?	-

Carroll test: 99 = best result, The Disabilities of the Arm, Shoulder and Hand Score (DASH): 100 = worst, The Hand Transplantation Score System (HTSS): 100 = best result.

Project: Hand transplantation
Appendix 4:3
Outcome variable: Hand sensory function

* + No or minor problems
? Some problems
- Major problems

Author, year, country	Study design	Number of patients n=	With drawals - dropouts	Hand sensory function					Comments	Directness *	Study limitations *	Precision *
				Two point discrimination (2 PD) (mm)	Semmes-Weinstein monofilaments testing (SWMF)	Modified Highet Scale (S0-S4) [1]	Protective Sensation	Cold / Hot Sensation				
Bernandon, 2015, France	Case-series	5 Uni/bi-lateral: 0/5	0	All regained static 2 PD between 6-15 mm (in 23 out of 50 digits)	Median (range): 3.61 (2.83-4.31)	Median S3+ (S3-S4)	n = 5	n = 5	Unclear follow period for SWMF test (table and text not corresponding) S3+ present in 56.6% median inervated fingers, 30% in ulnar innervated	+	+/?	-
Kaufman, 2011, USA	Case-series	6 Uni/bi-lateral: 5/1	3*	5-9 mm n = 1 pat	Not reported	Not reported	n = 4	n = 4	*Data not availible in 2 patients due to graft loss n=1, short follow up n=1	+	?	-
Pei, 2012, China	Case-series	11 Uni/bi-lateral: 8/3	0	1.5-6 mm* n = unclear	Not reported	Not reported	n = 11	Not reported	* Questionable values (ability to detect 1.5 mm in 2 PD)	+	?	-

[1] Highet scale: *S0:* no sensation.• *S1:* sensation to deep pain.• *S1+:* sensation to superficial pain.• *S2:* sensation to light touch.• *S2+:* hyperpathia.• *S3:* 2PD >15 mm.• *S3+:* 2PD 7–15.• *S4*: full sensation

Project: Hand transplantation
Appendix 4:4
Outcome variable: Complications

* + No or minor problems
? Some problems
- Major problems

Author, year, country	Study design	Number of patients n=	With drawals - dropouts	Complications					Comments	Directness *	Study limitations *	Precision *
				Graft loss	Infection	Rejection	Diabetes / glucose intolerance	Other				
Kaminska, 2014, Poland	Case-series	5 Uni/bi-lateral: 4/1	0	0	CMV infection (n=2) Acute tonsillitis (n=1) Herpes Zoster (n=1)	n=5	Not reported	Not reported	Same patients as in Chelmonski *et al*., 2015. Incongruence in CMV infections (n=1)	+	?	-
Kaufman, 2011, USA	Case-series	6 Uni/bi-lateral: 5/1	0	n=1	CMV infection (n=2)	n= 3 (+1)*	Diabetes (n=1)	Osteonecrosis of hips (n=1) Marginal zone lymphoma (n=1) Weight gain (n=1) Kidney dysfunction (n=1) Wound closure issues and poor vascularity (n=1)	* 3 patients with severe rejection episodes, and one with chronic rejection	+	?	-
Pei, 2012, China	Case-series	11 Uni/bi-lateral: 8/3	0	n=7*	CMV infection (n=1) Cutaneous mycosis (n=2) Pulmonary infection (n=1)	11 (in a majority once a year)	Hyper-glycemia (n=6)	Arterial thrombosis (n=1) Cushing's syndrome. (n=3) Hypoproteinemia (n=2)	* 6 hands removed because of non-compliance/no access to medication 1 hand removed because of unbearable pain	+	?	-

Project: Hand transplantation
Appendix 4:4
Outcome variable: Complications

* + No or minor problems
? Some problems
- Major problems

Author, year, country	Study design	Number of patients n=	With drawals - dropouts	Complications					Comments	Directness *	Study limitations *	Precision *
				Graft loss	Infection	Rejection	Diabetes / glucose intolerance	Other				
Petruzzo 2015, France	Case-series	5 Uni/bi-lateral: 0/5	0	0	Pat 2: Osteitis of ulna day 152. Pat 3: Epstein-Barr virus reactivation – asymptomatic Pat 5: Herpes zoster and oral cellulitis	n=5. all reversed	Pat 1 and 5 transient hyperglycemia Pat 2 and 3 Decrease in insulin clearance	Pat 1: Serum sickness in day 7 Pat 1 and 4: Osteopenia Pat 2 (day 1): Thrombosis of R ulnar artery. Osteoporosis Pat 3: Superficial and deep venous thrombosis after Campath-1H injection vascular Pat 5: Iatrogenic burning of hand Thrombosis (day 12) of L and R radial and L ulnar arteries. Alopecia areata. Creatinine deterioration 2 years post-tx.		+	?	-

CMV- Cytomegalovirus

Appendix 5

ETHICAL ANALYSIS OF HAND TRANSPLANTATION

Question	Answer/ comment
1. From the patient's perspective, how does this method/technology affect the patient's quality of life and life expectancy?	Hand transplantation has shown the ability to remarkably increase the patient's quality of life. The leverage of this gain is partly dependent on the individuals physical factors e.g. level of amputation, uni- or bilateral loss, functionality of remaining stump /-s. Restoring the anatomy of the upper extremity is of great concern for many amputees, but not only for its functional benefits. The loss of a hand results in a change in one's body perception, with the feeling of not being "whole", which often leads to a significant decrease in self-esteem. These feelings may convey to avoidance of social involvements in public as well as private levels. Hand transplantation is unique in that sense that recipient is able to consider the graft as the patient's own body part and not merely as a functional device and therefore restoring body image of completeness. Due to the need of life-long immunosuppressive treatment to prevent rejection there is a risk of shortening in life time expectancy. An estimation of three years have been considered in the Swiss HTA analysis. Patients are well informed about this possibility. From the patient's perspective it is important to be well informed about risks and benefits compared with osseointegrated prostheses.
2. How severe is the patient's need that the method/technology must meet?	Patients who suffer from amputation of one or both upper extremities are routinely treated by prosthetic replacement. Unfortunately, up to 20-30% of the patients are not able to cope with such treatment and do not use their prosthesis. Common complaints are heaviness, lack of sensation, sweat using the socket, and a sense of incompleteness. Hand transplantation represents for this category of patients the only opportunity to regain functionality, self-esteem, and reintegration in their social life. Bilateral- or especially quadriamputees are constantly dependent on care from others.
3. Does method/technology have any influence on how others view the patient (concerning humanity and human dignity), or on how the patient views himself or herself (concerning humanity and human dignity)?	The loss of one or both upper extremities has a tremendous impact on the life of a person. Common issues that affect the mental status of a patient are fear of the unknown, loss of self-esteem, loss of self-confidence, fear of rejection, and loss of occupational roles. A sense of pity is often perceived by the community and the patient itself. Hand transplantation gives the patient the possibility to improve most of these aspects, especially feeling as a 'whole' again. This aspect cannot be overemphasized. Functionality is often expressed by numbers that show how well a patient performs on a certain task. But only through careful interviews one can really appreciate psychosocial improvements, and understand that a sense of completeness, of regained social role, interaction with the public and human dignity has been restored after

	transplantation. This aspect, often hard to quantify, plays a remarkable role for these patients. Furthermore, besides the functional disability, being unable to work and to give his/her own contribution to the society is one of the reasons upper amputees have low scores on quality of life questionnaires. The possibility of returning to work is from the patients perspective as important reason to undergo hand transplantation.
4. Can method/technology affect the patient's ability and possibility to be independent?	Bilateral amputees depend on assistance to deal with intimate activities of daily living such as cooking, showering and dressing. The intention of hand transplantation is to regain the patient's lost abilities and enabling the patient's possibility of being autonomous again.
5. If implemented, does this method/technology require any special steps to not compromise the patient's autonomy?	Currently it is difficult to calculate the risk/benefit ratio of hand transplantation due to the low number of cases around the world. The patient should be well informed on all potential risks related to lifelong immunosuppressive therapy, and a time frame of at least 6 months for consideration must be provided.
6. How does this method/technology affect the patient's physical, moral and personal integrity?	In conventional solid organ transplantation the identity of the donor and the recipient is kept secret. This, among other, to prevent unhealthy reactions of indebtedness and obligation to the recipient and the donor family. Being first of its kind in Scandinavia, hand transplantation may attract special interest and publicity. If the secrecy is broken, the uniqueness of the procedure will automatically put the counterpart in a peculiar situation. The risk of such a situation is imminent why informing both the recipient and the donor family about this intricacy is vital. One cannot guarantee full protection to either the donor family, or the recipient that the identity of the counterpart is kept secret, but effort needs to promote it.
7. Is method/technology cost-effective?	The effectiveness of functioning hand, with sensation and the aesthetics of a normal body part cannot be compared with any available technology. The financial cost of the procedure is likely to be refunded if the patient is able to return to work and become autonomous. In previous studies, bilateral hand transplantation is considered cost-effective (Chung *et al*., 2010).
8. How does this method/technology affect resources?	It is unlikely that more than one transplant per year is performed. This will not affect existing resources in a notable matter.

Question	Answer/ comment
9. Is this method/technology in conflict with professional values?	Transplantation is commonly used in a lifesaving procedure. Although legalisation regarding transplantation does not avert organs to be used in a non-life saving procedure e.g. cornea transplantation in blind patients. Kidney transplantation was first introduced as a quality of life procedure but was later showed to reduce mortality and therefore is now considered as lifesaving. Hand transplantation is so far regarded as a quality of life procedure and does not go against professional values.
10. Does this method/technology change the role of the professional in relation to the patient?	It does not change the role of the professional but it puts a great responsibility of the professional to do a comprehensive evaluation and just selection of patients so the risk/benefit balance can be justified.
11. Does this method/technology affect, or does it put any new demands on, a third party?	The donor family will be affected in a new way as discussed in point 6. Because it is new implementation a special enquiry will be given the donor's family about deceased assumed will of donating his/her hands if not known, thus to lessen the feeling of truncation the donor will be fitted with cosmetic prosthesis after the donation.
12. Is there any legislation of relevance with regard to this method/technology?	A hand is stated as an organ by “The Health and Social Care Inspectorate” (IVO) and accommodated within present regulations surrounding organ transplantation. Data on fingerprints will be checked with police department and the “fingerprints-identity” will be transferred to the recipient.
13. Is there any risk of conflict between the procedure of this method/technology and values of the society, or values of different groups?	Groups that find solid organ transplantation wrong are assumed to be against hand transplantation. Some may have the opinion that transplantation, as well as all health care, should solely engage in life saving procedures. Some may also find visibility of a transplanted organ repellent and feel disturbed by the procedure. For those in favour of transplantation, hands will be an additional organ to grant somebody with, increasing the number of organs able to donate.
14. Is there a risk that an introduction of this method/technology will cause a conflict with particular interests?	Because of the potential complications some may advocate prosthesis as the only conceivable treatment regardless of the possible benefits. On the contrary amputated patients that are not considered favoured by the procedure may have hard to accept being denied transplantation (e.g. due to underlying medical and psychiatric issues).

Question	Answer/ comment
15. Can an introduction of the method/technology influence the trust of the health care system?	The trust of the health care system should not be at risk. It is important that correct information is given to public about the circumstances surrounding the procedure and the legislations, as well as the benefits for amputated patients resulting from transplantation.
CONCLUSIONS	In contrast to solid organ transplantation hand transplantation is a quality of life procedure – not lifesaving, demanding in-depth risk/benefit analysis as well as comprehensive understanding of these judgements by the individual patients. Cost-effectiveness is hard to calculate but is considered to be in favour of hand transplantation compered to existing technology (prosthesis) in cases with bilateral amputation. Hand transplantation as a treatment requires no new legislation. The hand is defined as an organ and falls within existing regulations. Current laws and regulations for organ transplantations apply for hand transplantation. Taken together there are no strong ethical arguments against hand transplantation, instead there are great benefits for the patient to obtain in terms of both autonomy and quality of life.

Region Västra Götaland, HTA-centrum

Health Technology Assessment
Regional activity-based HTA

HTA

Health technology assessment (HTA) is the systematic evaluation of properties, effects, and/or impacts of health care technologies, i.e. interventions that may be used to promote health, to prevent, diagnose or treat disease or for rehabilitation or long-term care. It may address the direct, intended consequences of technologies as well as their indirect, unintended consequences. Its main purpose is to inform technology-related policymaking in health care.

To evaluate the quality of evidence the Centre of Health Technology Assessment in Region Västra Götaland is currently using the GRADE system, which has been developed by a widely representative group of international guideline developers. According to GRADE the level of evidence is graded in four categories:

High quality of evidence	= (GRADE⊕⊕⊕⊕)
Moderate quality of evidence	= (GRADE ⊕⊕⊕O)
Low quality of evidence	= (GRADE ⊕⊕OO)
Very low quality of evidence	= (GRADE ⊕OOO)

In GRADE there is also a system to rate the strength of recommendation of a technology as either “strong” or “weak”. This is presently not used by the Centre of Health Technology Assessment in Region Västra Götaland. However, the assessments still offer some guidance to decision makers in the health care system. If the level of evidence of a positive effect of a technology is of high or moderate quality it most probably qualifies to be used in routine medical care. If the level of evidence is of low quality the use of the technology may be motivated provided there is an acceptable balance between benefits and risks, cost-effectiveness and ethical considerations. Promising technologies, but a very low quality of evidence, motivate further research but should not be used in everyday routine clinical work.

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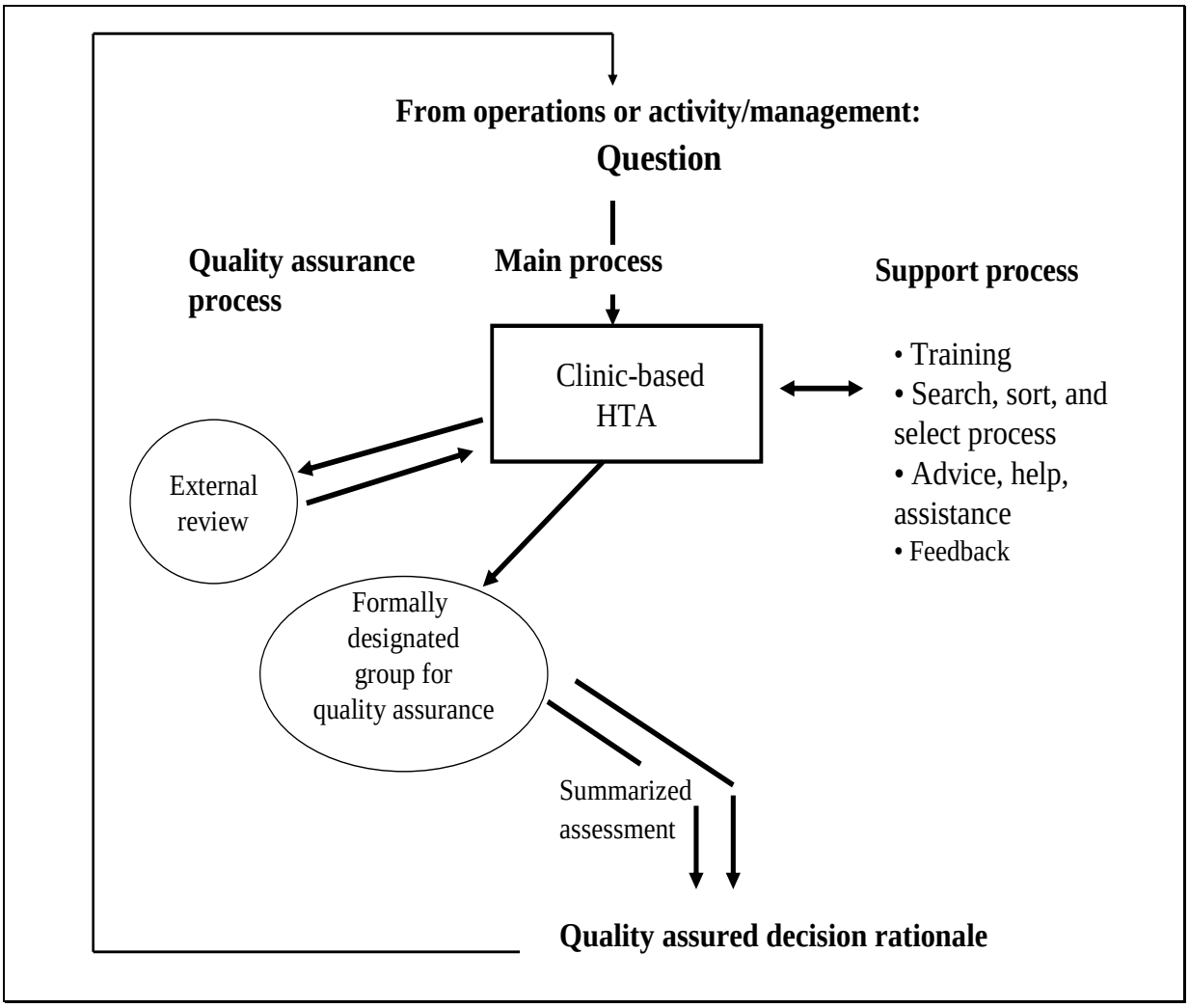
From operations or activity/management:
Question
Quality assurance process
Main process
Support process
Clinic-based HTA
• Training
• Search, sort, and select process
• Advice, help, assistance
• Feedback
External review
Formally designated group for quality assurance
Summarized assessment
Quality assured decision rationale

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