HTA REPORT

Prostheses for primary total knee replacement in Italy

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HTA REPORT

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Foreword

This year Agenas has produced two Health Technology Assessment (HTA) reports for the Ministerial Committee on Medical Devices (CUD). The present report analyses the best and most appropriate evidence of costs and effects of what has become a commonly used procedure in the Italian NHS and worldwide: total knee replacement or TKR.

The report and its content are as always the product of a long and laborious process involving consultation with experts, referees, producers and other stakeholders.

Perhaps the most interesting feature is the attempt to construct cost-effectiveness ratios using Italian data and testing the sensitivity of the conclusions with data from a very large and long-established TKR register: that of Australia. The great advantage of cost-effectiveness ratios is that they allow rational and explicit decisions to be made, or at least they present the evidence in an easily understood "bottom line".

The limits are due to the sparseness of some of the data and the constraints on the utilisation of available data as illustrated graphically in the Discussion section. For example in this report Agenas proposes the construction of relatively simple and quick incremental cost effectiveness ratios (ICERs) by using the expedient of surveying what models of prostheses are available, determining their average acquisition cost and then dividing the total by the 5-year survival rate. The result, applied to the number of procedures compared against the baseline pair-wise, one prosthesis at a time by model and design class, allows ICERs to be calculated using Italian data (the most effective prosthesis according to Emilia-Romagna's RIPO – one of the possible sources of effectiveness estimates, but the only one available in Italy). The snag is that at present there is only one Italian source of effectiveness data. Data on models used in Emilia-Romagna may not be usable in other regions (and vice-versa) limiting the usefulness of this method. However Agenas believes that the report shows why price, activity and data on effectiveness (together with patient-centred outcome data such a quality of life measures) should be routinely collected nationwide. It also shows the potential of the HTA process for empowering decision-makers to take ethical decisions.

Fulvio Moirano

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Prefazione

Quest'anno l'Agenas ha prodotto, su mandato della Commissione Unica Dispositivi Medici (CUD), due report di Health Technology Assessment (HTA). Il presente report analizza le migliori evidenze circa i costi e gli effetti di una delle più comuni procedure effettuate dal Servizio Sanitario Italiano e nel mondo: la sostituzione totale di ginocchio.

Tutto il report è, come sempre, il prodotto di un lungo e laborioso processo di consultazione con esperti, revisori, produttori e altri stakeholder.

Ciò che caratterizza il presente report di HTA è il tentativo di costruire indicatori di costo-efficacia utilizzando dati rilevati in Italia, testando le conclusioni anche con dati provenienti da un ampio e consolidato registro di artroplastica: quello dell'Australia. Il grande vantaggio di costruire indicatori di costo-efficacia è che essi consentono di prendere decisioni razionali ed esplicite, o che presentino evidenze facilmente fruibili.

I limiti del presente lavoro sono dovuti essenzialmente alla scarsità di alcuni dati ed ai vincoli nell'utilizzo dei dati disponibili, come illustrato graficamente nel capitolo delle discussioni.

L' Agenas propone la costruzione di indicatori incrementali di costo efficacia (ICER) semplici e di facile calcolo, utilizzando l'indagine condotta sul territorio nazionale per la rilevazione delle tipologie di protesi disponibili e il loro costo medio d'acquisto e dividendo il totale per il tasso di sopravvivenza a 5 anni. Il risultato, confrontando la protesi base line (la protesi più efficace in base ai dati raccolti dal RIPO- Emilia Romagna - una delle possibili fonti di stima dell'efficacia ma attualmente unico fruibile in Italia) con gli altri modelli appartenenti alla stessa classe, permette di calcolare gli ICER utilizzando dati italiani. La criticità è rappresentata dall'esistenza, in Italia, di una sola fonte di dati per l'efficacia ed i dati sui modelli di protesi utilizzati in Emilia-Romagna possono non essere utilizzabili in altre regioni (e viceversa) e quindi limitare l'utilità di questo metodo. Tuttavia l' Agenas crede che il report dimostri il motivo per cui i dati di prezzo, volume e efficacia (tenuto conto della centralità del paziente e delle relative misure di outcome come la qualità di vita) dovrebbero essere sistematicamente raccolti a livello nazionale. Esso mostra anche il potenziale del processo di HTA di responsabilizzare i decisori politici a prendere decisioni etiche.

Fulvio Moirano

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Executive summary

One-liner

Decision makers should privilege, in their activities, the use of the more cost-effective prosthesis models, linking purchase price with effectiveness estimates.

Background

Total knee replacement (TKR) is known as an effective procedure for patients with osteoarthritis (OA). The wide array of prosthesis models on the market makes the issuing of evidence-based guidance on choice, a priority for the equitable and transparent use of resources in any health system.

The assessment of the clinical value of each model, from the viewpoint of a national health system, requires data on:

i) which models are used in practice;

ii) acceptable estimates of performance for those models;

iii) their price.

Aim

We aimed to identify the TKR prostheses currently used in Italy, to retrieve evidence of performance for all the models identified from clinical studies and arthroplasty registers, and to construct a cost-effectiveness model to support the choice for healthcare payers.

Methods

We first performed a context-specific analysis to identify which prosthesis models are currently in use and their purchase prices. We involved 172 public hospitals and private accredited providers of the Italian national health service.

Then we carried out a systematic review of evidence from clinical studies and an analysis of implant performance from arthroplasty registers. We were interested in recipients aged 50 and above that had received primary TKR and had been followed for at least 5 years.

Finally, with the purchase prices and the effectiveness estimates identified, we carried out an economic evaluation to compare the different models.

Results

Literature in this field was too generic to answer our research questions. Very few studies met our inclusion criteria (4 primary and one registry-based studies) and those that did were poorly reported. For this reason we decided to give more weight to performance estimates from periodic reports of the arthroplasty registers. We received full collaboration by one national and one regional register (the Australian AOAJRR and the Emilia-Romagna RIPO respectively). Unfortunately, heterogeneity of reporting formats and attitudes, and low data-sharing ethos, caused a sizeable loss of data on costs and effectiveness. We were unable to make all the planned comparisons.

According to our calculations the most cost-effective among the prostheses with multiradius femoral design is NEXGEN LPS (ZIMMER), whereas SCORPIO (STRYKER) is the most cost-effective single-radius prosthesis. Little can be said for the remaining models, but our ICERs (incremental cost-effectiveness ratios) provide at least some benchmarking for similar prostheses with sufficient survival data in the future.

Conclusions

Despite the limitations and constraints of our study we were able to show that purchase price and effectiveness are not sufficient to inform decision makers. What is required is the linking of the two into ICERs within prosthetic design classes. It is essential however that performance is calculated on recipient populations which are broadly similar in terms of age, gender, indications and whenever possible, BMI.

Sintesi

Problema clinico e indicazioni per la sostituzione totale del ginocchio

L'artrosi è una malattia cronico degenerativa delle cartilagini articolari. Colpisce soprattutto i soggetti anziani e prevalentemente quelli di sesso femminile. Alcune articolazioni sono più suscettibili nello sviluppare questa patologia. La gonartrosi, ovvero artrosi del ginocchio, è una delle più comuni forme di artrosi. Il danneggiamento della cartilagine che ricopre la superficie dell'osso è responsabile di una sempre più ridotta capacità di movimento dell'articolazione e di un progressivo aumento del dolore. Il primo approccio terapeutico, nella maggior parte dei soggetti, consiste in una terapia farmacologica mirata a ridurre infiammazione e dolore. Considerata la natura progressiva della patologia, molti pazienti, dopo un iniziale gestione medica, sono sottoposti al trattamento chirurgico.

La sostituzione totale di ginocchio (TKR) è l'intervento più comunemente effettuato per la gonartrosi e una delle procedure chirurgiche ortopediche più comunemente effettuate in Italia e nel mondo. La procedura è caratterizzata da ottime probabilità di successo ed è in genere risolutiva. I dati SDO mostrano che nel periodo 2001-2005 il numero di pazienti dimessi per sostituzione totale di ginocchio (codice ICD-9-CM 81.54) è significativamente aumentato passando da 26.793 a 44.119. È prevedibile che nel futuro si riscontri un incremento nel numero di procedure effettuate poiché l'età media della popolazione trattata è in diminuzione mentre l'aspettativa di vita è in aumento.

Descrizione della procedura e della tecnologia

L'intervento primario di TKR prevede la resezione di precise porzioni di tessuto osseo e legamenti allo scopo di creare delle superfici adatte per il posizionamento e il fissaggio del sistema protesico. Il fissaggio in sede può essere ottenuto mediante cementazione, tecniche press-fit o con metodi ibridi.

La valutazione di tali sistemi, classificati come dispositivi medici di Classe III e denominati protesi tri-compartimentali o, più comunemente protesi totali di ginocchio, rappresenta l'oggetto del presente report di Health Technology Assessment (HTA).

In commercio sono disponibili diversi tipi e modelli di protesi di ginocchio ma tutti hanno in comune i seguenti elementi:

- una componente femorale in metallo;
- una componente tibiale in metallo;
- un inserto in materiale plastico che permette l'articolazione tra la componente femorale e quella tibiale.

Talvolta l'intervento prevede anche la sostituzione della rotula con una in materiale plastico o in plastica e metallo. La scelta delle protesi è basata su alcune caratteristiche del paziente (es. età, livello di attività fisica), su caratteristiche dell'impianto (es. tipo, modello), sull'esperienza del chirurgo e sulla sua familiarità con il dispositivo. L'offerta sul mercato è abbastanza ampia e i sistemi protesici possono essere classificati sulla base di diversi parametri: metodo di fissaggio delle componenti; possibilità di conservare il legamento crociato posteriore; caratteristiche progettuali; tipo di inserto.

Obiettivi del report

L'intervento di TKR non è esente da complicanze che possono insorgere a breve termine (ad es. mobilizzazione dell'impianto, infezione) o a lungo termine (ad es. usura dell'inserto). Spesso le complicanze richiedono la rimozione dell'impianto o la sostituzione di una sua parte mediante una ulteriore procedura chirurgica denominata revisione dell'impianto. La revisione ha un impatto notevole sia in termini clinici che economici.

Il modello protesico è sicuramente una delle variabili che incide sull'esito dell'intervento primario di TKR e sui suoi costi.

La policy question del presente report di HTA è la seguente:

Le protesi per la sostituzione primaria totale di ginocchio utilizzate nella pratica clinica italiana, sono supportate da sufficienti evidenze? È possibile correlare la performance del dispositivo al suo prezzo d'acquisto?

Le domande di ricerca, in accordo con la policy question, sono pertanto le seguenti:

- quali sono le protesi di ginocchio utilizzate in Italia?
- quali sono le evidenze di efficacia e sicurezza provenienti da studi clinici pubblicati delle protesi di ginocchio utilizzate in Italia?
- quali sono le evidenze di efficacia provenienti dai registri di artroplastica delle protesi di ginocchio utilizzate in Italia?
- quali sono i costi di ciascun modello di protesi?
- quali sono gli indicatori di costo-efficacia delle protesi di ginocchio utilizzate in Italia?

Gli obiettivi principali del presente report sono i seguenti:

- identificare e descrivere le protesi utilizzate in Italia;
- condurre un'analisi dei prezzi dei modelli individuati;
- identificare e valutare le evidenze disponibili in merito all'efficacia e alla sicurezza dei modelli individuati;
- raccogliere stime di efficacia dai registri di artroplastica relativamente ai modelli individuati;
- costruire un modello di costo-efficacia per la valutazione comparativa dei modelli individuati.

Metodi

L'analisi di contesto ha preceduto le altre fasi del lavoro. Attraverso una survey presso le strutture del SSN che effettuano la procedura di TKR, sono state raccolte informazioni relative ai volumi e ai costi di acquisto delle protesi totali di ginocchio negli anni 2006 e 2007. È stata effettuata una stratificazione delle strutture per numero di procedure effettuate e posizione geografica e, successivamente sono state estratte casualmente 152 unità campionarie (Aziende Ospedaliere, Presidi Ospedalieri, Strutture private accreditate e Istituti di Ricovero e Cura a Carattere Scientifico).

Tutti i modelli individuati dalla survey sono stati associati ad un prezzo medio ponderato sul volume acquistato che sono stati utilizzati successivamente per la costruzione delle stime di costo-efficacia per tipologie di protesi comparabili.

L'efficacia di tali modelli di protesi (intesa come tasso di revisione o tasso di sopravvivenza dell'impianto) è stata ricercata utilizzando due metodi differenti: la revisione sistematica della letteratura scientifica pubblicata e la consultazione dei registri di artroplastica di diverse nazioni europee ed extraeuropee.

La revisione sistematica della letteratura è stata condotta utilizzando come parole chiave i modelli di protesi così come derivanti dalla survey. I criteri di inclusione degli studi erano rappresentati da età minima del gruppo di pazienti di 50 anni e 5 anni minimo di follow-up.

La consultazione dei registri di artroplastica per i medesimi modelli e con gli stessi criteri (età, follow up e indicazione clinica) è stata condotta sia attraverso l'analisi dei rapporti periodici pubblicati che attraverso richiesta diretta ai coordinatori di ulteriori informazioni, quando tali rapporti non presentavano i dati nel formato a noi utile.

Per facilitare l'analisi comparativa, tutti i modelli individuati sono stati collocati all'interno di 5 classi secondo un parametro caratterizzante la biomeccanica articolare: protesi con componente femorale a raggio di curvatura multiplo; protesi con componente femorale a raggio di curvatura singolo; protesi a pivot mediale; protesi con componente femorale tricondilare; sistemi vincolati e a cerniera.

La valutazione di costo efficacia è stata condotta attraverso la costruzione di un semplice indicatore di costo efficacia incrementale (ICER) volto alla comparazione delle protesi di ginocchio aventi caratteristiche biomeccaniche assimilabili. Tale indicatore indica il costo aggiuntivo di una protesi rispetto ad un'altra in termini di revisione evitata.

Risultati

L'analisi di contesto ha permesso di individuare 39 diversi modelli di protesi di ginocchio che sicuramente sono state acquistate dalle strutture del SSN. All'interno del campione osservato, la maggior parte delle procedure sembra essere stata effettuata con soli 6 modelli di protesi: NEXGEN (ZIMMER), SCORPIO (STRYKER), PROFIX (SMITH & NEPHEW), GENESIS II (SMITH & NEPHEW), LCS (DEPUY), VANGUARD (BIOMET). Per 34 dei 39 modelli individuati è stato possibile calcolare il prezzo per sistema protesico ponderato per volume d'acquisto.

Per quanto riguarda le evidenze di efficacia, la letteratura scientifica si è mostrata troppo generica per il nostro specifico quesito di ricerca. Solo un esiguo numero di studi erano compatibili con i nostri criteri di inclusione (4 studi primari e uno studio basato su registro) e il reporting si presentava spesso scarso o in maniera non chiara. Per tali motivi è stato deciso di non considerare le evidenze da studi clinici e di privilegiare l'utilizzo esclusivo delle stime di efficacia calcolate dai registri di artroplastica.

Hanno pienamente collaborato al presente progetto soltanto due registri: uno nazionale (l'AOAJRR Australiano) e uno regionale italiano (il RIPO dell'Emilia-Romagna). L'eterogeneità dei

formati e delle variabili raccolte e presentate, unite allo scarso spirito di partecipazione dimostrato da alcuni coordinatori, hanno portato ad una considerevole perdita di dati, pertanto non è stato possibile effettuare tutte le valutazioni comparative previste.

La valutazione di costo efficacia ha risposto al tentativo di unire i dati di costo delle protesi con i dati di efficacia provenienti dai registri. I rapporti incrementali di costo efficacia (ICER) sono stati costruiti come rapporto tra le differenze di costo e di efficacia tra due protesi appartenenti alla stessa classe femorale confrontando la protesi più efficace (baseline) con le altre. Secondo quanto calcolato con i dati a nostra disposizione, tra le protesi con componente femorale a raggio di curvatura multiplo, la NEXGEN LPS (ZIMMER) è il modello con maggiore costo-efficacia considerando le stime di efficacia di entrambi i registri, mentre la SCORPIO (STRYKER) risulta essere la più costo-efficace tra quelle con componente femorale a raggio di curvatura singolo. Interessante a tal fine, seppur esulando dagli obiettivi del presente report, è la costruzione dei rapporti di costo efficacia (ICER) per analisi sub regionali, privilegiando in questo caso la variabilità dei prezzi. Nessuna considerazione può essere fatta sui modelli appartenenti alle altre classi ma i valori degli ICER possono essere utilizzati come riferimento per la comparazione di modelli simili e costituire un facile strumento di calcolo per tutti i decisori a tutti i livelli decisionali.

Discussione

Nonostante esistano alcuni limiti e vincoli, il presente studio ha dimostrato che le sole informazioni sul prezzo di acquisto dei sistemi protesici non sono sufficienti ad orientare le scelte dei decisori. Di maggiore utilità pratica sembra essere la combinazione del prezzo di acquisto con stime di efficacia attraverso degli indicatori ICER che tengano conto di gruppi di modelli con caratteristiche analoghe. È comunque essenziale calcolare le stime di efficacia tenendo conto di tutta la popolazione ricevente e di alcuni parametri fondamentali (ad es. età, sesso, indicazione clinica, indice di peso corporeo).

Raccomandazioni

La scelta delle protesi totali di ginocchio da utilizzare dovrebbe essere fatta tenendo fortemente in considerazione le evidenze di buona performance provenienti dai registri di artroplastica. Le esperienze di altre nazioni e alcune esperienze regionali italiane dimostrano come la creazione di un registro nazionale dell'implantologia del ginocchio sia una fondamentale esigenza per il SSN che si confronta con i problemi della qualità degli interventi sanitari e della sostenibilità.

1. Background

1.1 Total knee replacement: indication and clinical problem

Osteoarthritis (OA) is one of the most common indications for total knee replacement (TKR). OA is caused by the damage of the cartilage covering bone surfaces, resulting in a joint which no longer moves normally. There is usually a progressive increase in pain reported by the patient as the cartilage degenerates. Initially treatment focuses on drug therapy to reduce inflammation and pain[1].

Knee replacement may also be considered for rheumatoid arthritis or other inflammatory joint diseases or following injury. There is a wide variation in the types of prostheses. There is an expected increase in the utilisation of knee arthroplasty in the future due to a lowering in the average age of intervention, and an increase in the prevalence of OA as the population ages and life expectancy increases.

Evidence suggests that women are twice as likely to undergo TKR as men, this could be mainly attributed to gender-oriented diseases and a higher prevalence of OA amongst women[2].

The intervention of knee replacement is not without problems and complications can arise both in the short term such as stiffness, instability or infection and the long term such as prosthesis wear and aseptic loosening. Complications often result in pain. If one of these complications occurs, the successive step is the substitution or revision of the failed implant. Revision surgery is less successful than primary intervention, has a negative impact on the patient's quality of life, and represents a burden to the National Health Service.

However it is unclear if obesity and gender are factors directly linked to TKR outcomes as there is conflicting evidence[2,3]. One of the most important factors affecting outcome is age. The younger the patient at the time of primary surgery, the higher the subsequent revision rate. This is almost certainly a reflection of higher activity levels. Some studies suggested that higher numbers of knee replacements performed by the surgeon and by the hospital annually (throughput), lead to better outcomes and a lower likelihood of complications[2].

1.2 Epidemiological data and population

Primary knee replacement is one of the most common surgical orthopaedic procedures undertaken in Italy today. The data from international registries show that the knee replacement procedures (total knee replacement and revision) are very common and mainly involve females aged 65 years or more[4-8]. These data refer only to patients in the registries' survey but are very representative because the coverage rate is generally high (around 90%). Other studies show the same trends for age and gender[9-10].

We analysed the frequency of these procedures in Italy carrying out an analysis of the SDO database (SDO - hospital discharge records)[11] owned by the Ministry of Labour, Health and Social Policy (MLHSP).

The aim was to gather data regarding the number of patients discharged for primary total and revision knee replacement procedures, aged 50 and over (those most likely to have OA of the knee) from 2001 to 2005.

The procedures were identified according to ICD-9-CM classification (code 81.54 for primary TKR and code 81.55 for revision of knee replacement). ICD-9-CM 81.54 codes for unicompartmental knee replacement (UKR) thus volumes are cumulative for both procedures. The TKR codes refer to both the TKR and UKRprocedures.

The analysis showed that the number of patients discharged for TKR in 2001-2005, increased from 26,793 to 44,119, whilst the number of patients discharged after revision increased from 1,166 to 2,309. (Figure 1.1)

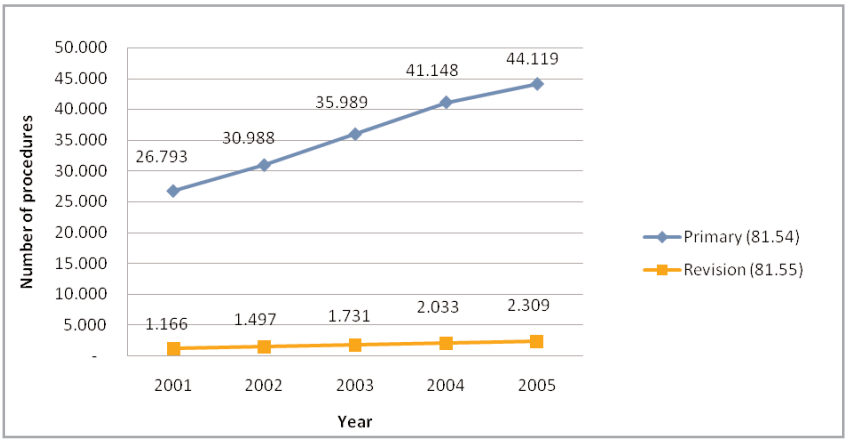
The increase in total knee replacements remained constant in the first 4 years but decreased slightly in 2005 (from an annual increase of approximately of 15% to an increase of 7% in 2005). The revision procedure increased by approximately 15,5% apart from the first year (2001) in which there was an increase of 28%. The revision data cannot be broken down from the data on total knee replacement because the SDO database does not allow the linking of revision procedures with the original intervention.

Focusing on TKR, the object of this report, we analysed the geographical distribution in Italy and the age and gender of the patients involved in these procedures.

Considering the distribution of the Italian regions in macro areas of Italy (North, Centre, South and Islands, i.e. Sardinia and Sicily)[12], the data show that Northern Italy (population around 12 million aged 45 years and older) accounts for the highest number of TKR procedures, with a total number of interventions greater than the remaining macro areas summed together having approximately the same population (Figure 1.2). However, Figure 1.2 does not take into account the possibility that patients living in one region might be treated in another, thus possibly increasing numbers in some regions while decreasing in others.

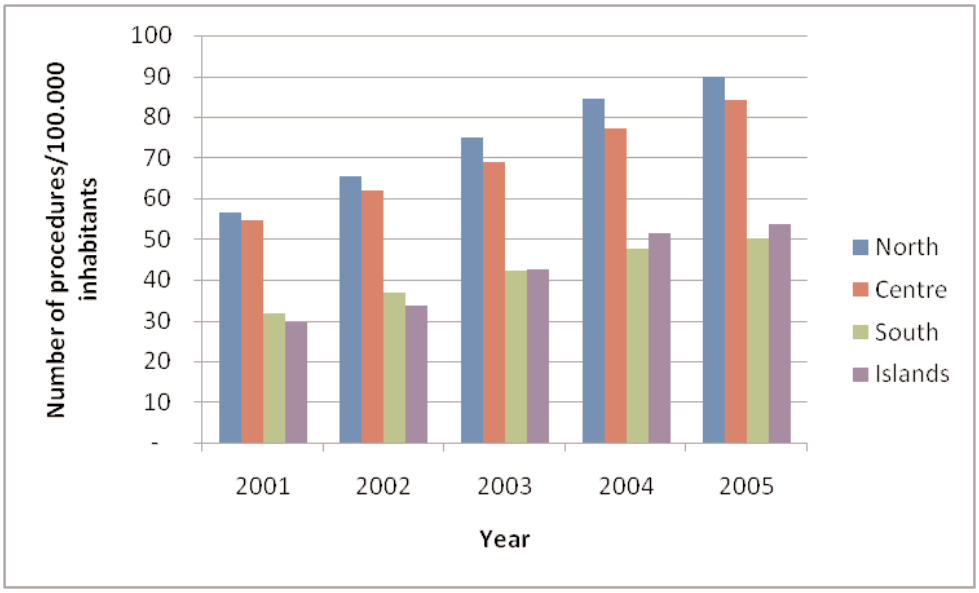
The majority of patients who undergo this procedure are females (75%) aged 65 to 74 years (Figure 1.3), but in 2001-2005 there was an increase in the age group 45-64.

Figure 1.1: Number of procedures performed for primary (ICD-9-CM 81.54) and revision (ICD-9-CM 81.55) knee replacement.



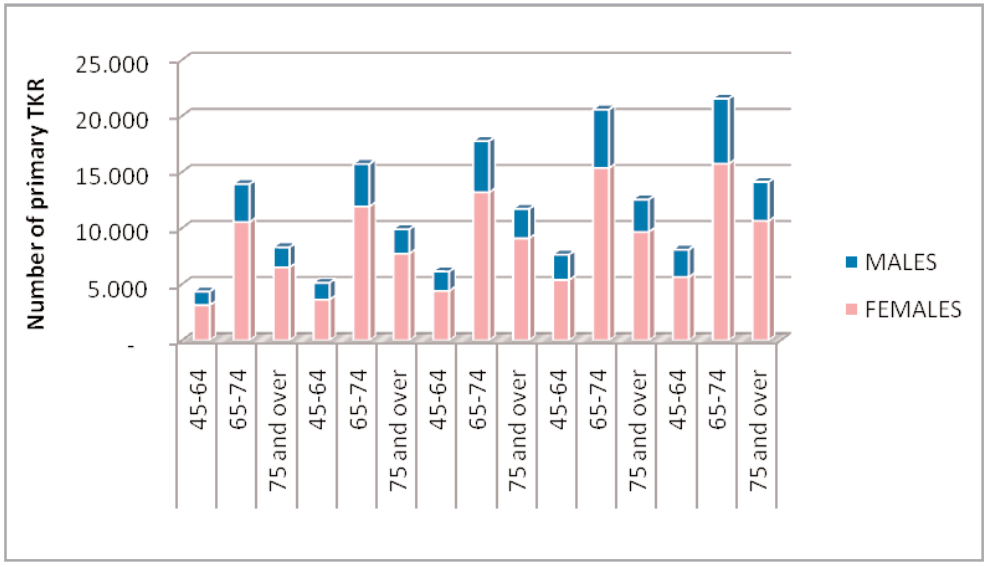
Source: SDO database

Figure 1.2: Distribution of TKR in the geographical areas of Italy.



Source: SDO database.

Figure 1.3: Distribution of TKR for age and gender groups.



Source: SDO database.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2. Technology, procedure and alternatives

2.1 The technology

Tri-compartmental knee prostheses, total knee prostheses or total knee implants (also called knee systems) are those in which all the compartments of the joint (medial, lateral and patello-femoral) are replaced. Unicompartmental (or unicondylar) are used for the replacement of only one of the femoral condyles, whereas patello-femoral prostheses are used for the replacement of the patello-femoral compartment only[13,14].

This report is focused on the prostheses for primary TKR only. Unicompartmental or patello-femoral designs will not be assessed or mentioned in this report.

The knee is a complex biomechanical joint since the articulating surfaces roll and glide as the knee bends and straightens. The large muscles of the leg provide strength while ligaments provide stability to the articulation. Three bones are involved in the knee: the femur, the tibia and the patella. The articular cartilage covers the bearing surfaces and when it becomes damaged, pain occurs[15,16].

The first designs of artificial knee joints adopted the concept of a hinge mechanism between the components. More recent designs, recognising the biomechanics of the joint, attempt to emulate the complex movements and attempt to take the maximum advantage in support coming from ligaments.

Many types of total knee implants are commercially available, but all have in common the following:

- a femoral component: a large block used to cover the resected distal part of the femur. The metallic part "resurfaces" the bone and has an internal groove in which the patella slides up and down permitting bending and straightening.
- a tibial component: a metallic or plastic plate (also called tibial tray) that is applied to the proximal tibia by a central stem or pins.
- an insert: a plastic block that allows the femoral component to articulate with the tibial component. It can have a complex profile that mimics the natural articular surface and may present a central ridge.
- a patellar component: a small round plastic "button" having the shape of the natural patella.

The choice of the prosthesis is based on the patient's characteristics (e.g. age, weight, activity level), the implant's characteristics (e.g. design, materials), and the surgeon's experience and familiarity with the device. Cobalt-Chrome alloys are the most commonly used for the femoral and tibial component but some models have a Titanium alloy tibial component. Cementless systems generally have hydroxyapatite or porous titanium surface coatings. The inserts are usually made of UHMWPE (Ultra-High Molecular Weight Poly-Ethylene) whilst the patellar component may be all-plastic or metal-backed and fixed with or without cement[14,17,18].

Prostheses for TKR can be classified taking into account several variables:

- the method of fixation of the components (cemented, uncemented or hybrid);
- the retention of posterior cruciate ligaments (cruciate retaining or CR design) or their sacrifice (posterior stabilised or PS design);
- the bearing mobility (fixed or mobile bearing);
- the profile of the femoral component (multiradius design, single-radius design, medial pivot design or others).

Evidence and trends related to the use of a particular design instead of others are in Appendix 1.

2.2 The procedure

TKR is a bone resecting and resurfacing procedure. Specific sets of instrumentations and tools are used to create exact surfaces to accommodate the implant. The knee joint can be approached anteriorly (through a medial parapatellar approach), or by mid-subvastus approach. Osteophytes and intra-articular soft tissues are then cleared. Bone cuts in the distal femur are made perpendicular to the mechanical axis, usually using intermedullar alignment systems. The proximal tibia is cut perpendicular to the mechanical axis of the tibia using either intermedullar or extramedullar alignment rods. Restoration of mechanical alignment is important to allow optimum load sharing and prevent eccentric loading through the prosthesis.

Sufficient bone is removed so that the prosthesis re-creates the level of the joint line. This allows the ligaments around the knee to be balanced accurately and prevents alteration in patella height, which can have a deleterious effect on patellofemoral mechanics. Patellofemoral tracking is assessed with trial components in situ. If the patellofemoral joint is significantly diseased, it can be resurfaced with a polyethylene "button". If a cemented system is chosen, the definitive components that have been selected are cemented into place by bone cement (polymethylmethacrylate, PMMA). Uncemented systems are fixed with a press-fit fixation process[19,20].

2.3 The alternatives

Most commonly, TKR is performed for OA of the knee. Initial management of most patients with OA can be non-operative and may include nonsteroidal anti-inflammatory medications, intra-articular viscosupplementation, analgesics, bracing, orthoses, shoe modifications, weight loss, and ambulatory aids. Activity modification and home health care-assistive devices may also be necessary. Joint aspiration and intra-articular steroid injection may be used to improve synovitis. Because of the progressive nature of OA, many patients receive operative treatment after an initial medical management[19]; however TKR should not be undertaken unless a patient has received full conservative management and that management is no longer controlling the patient's discomfort. As the focus of this report is on TKR, non-surgical alternatives to TKA will not be considered as well as other types of arthroplasty (unicompartmental and patello-femoral knee arthroplasty).

3. The marketing status of knee prostheses and current reimbursement arrangements in Italy

In Italy, the legal framework for knee total joint replacement approval (as for all medical devices) is based on Legislative Decrees, implementing the EU Directive 93/42/EEC and its successive amendments. In addiction the requirements made in the so called "up classification" Directive and the legislative decree transposing it specifically apply to knee prostheses. These rules regulate every different type of medical devices and require specific and detailed essential data on technical performance, effectiveness and safety of the device and its production process (design manufacture and quality control). Finally to be allowed to be placed and put into service on to the Italian market, the product must bear a CE-mark. According to the above indicated regulations knee total joint replacements are classified as Class III devices.

After the approval process, each device is marked as a CE device and distributed in Italy by national and international companies and/or exclusive distributors.

Recently, in addition to a national database of all registered medical devices available in Italian market, the MLHSP has created the "Repertorio generale dei Dispositivi Medici" (RDM). This is a notification system requesting more information about each device being sold in Italy.

Since 1995, hospitals have been paid on the basis of DRGs (diagnosis related groups) replacing a system of per diem payment. Each region has the power to determine and update reimbursement fees[21]. The fees for hospital surgical procedures with ceiling (maximum prices) have been fixed by the MLHSP, and generally include costs related to the operating room (personnel, materials, drugs, prosthesis, and indirect costs of the operating room) and the costs linked to the hospitalisation of the patient (DM 14.12.1994).

In 2006, a new national DRG system was introduced (with the possibility for regional variation) and the MLHSP has given the freedom to modify DRGs' fees. Additional payments can also be used to supplement DRG payments: in this case, the region must carry the burden of the difference (DM 12.09.2006).

A report on the regional health fund allocation system and payment of hospitalisations[22] has shown that in the year 2008 in the 15 regions observed (Piemonte, Valle D'Aosta, Lombardia, Veneto, Friuli Venezia Giulia, Liguria, Emilia Romagna, Toscana, Umbria, Marche, Lazio, Campania, Puglia, Basilicata e Sicilia) the cost of the knee prosthesis is included in the fixed fee for TKR with the exception of:

- Lombardia: there is an additional payment of 25% of the average cost of prosthesis;
- Puglia: hospitals can choose between a regional fixed fee (including the price of prosthesis) or a reduction of 20% of fixed fee plus the cost of the prosthesis.

4. Objectives, policy and research questions

The *policy question* of this HTA report was the following:

Are the prostheses for total knee replacement (TKR) currently used clinical practice in Italy supported by sufficient evidence? Can performance of the devices be linked to their price?

This policy question can be broken down into the following *research questions*:

- Which prostheses for TKR are used in Italy?
- What is the evidence of effectiveness and safety from the literature of TKR prostheses used in Italy?
- What is the evidence of effectiveness from registers of TKR prostheses used in Italy?
- What are the costs of each single prosthesis model?
- What are the cost effectiveness indicators of the TKR prostheses used in Italy?

The following main *objectives* were used to draft this report:

- to identify and describe the TKR prostheses currently used in Italy ("context");
- to retrieve and assess the available evidence about effectiveness and safety of the prostheses for primary TKR used in Italy;
- to collect TKR prostheses data on effectiveness and safety from arthroplasty registers;
- to compare TKR prostheses performance from published studies with data from arthroplasty registers;
- to carry out an economic analysis of the TKR prostheses prices in Italy;
- to create a cost-effectiveness model for the evaluation of the TKR prostheses and their performance.


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5. Context-specific analysis

Context specific analysis was important to determine the utilisation and costs of knee prostheses among the centres of the Italian National Health Service (INHS). The aim of this chapter was to offer an impact scenario of utilisation of knee prostheses, in terms of diffusion and purchasing costs. We carried out a survey to collect data on the prostheses used in Italy, prices and volume of activity. The cost-effectiveness analysis are presented in Chapter 8. We also contacted the association of producers and distributors of medical devices (ASSOBIOMEDICA) and the Istituto Superiore di Sanità (ISS, the Italian equivalent to the NIH) for collaboration and technical support.

5.1 Methods for contextual analysis: national survey

As there is no central register of TKR prostheses currently on the Italian market, we carried out a survey to gather data on prostheses currently used in Italy, their purchasing prices and activities volume by means of a structured questionnaire (Appendix 2) sent to public hospital services and private accredited providers of the INHS.

Information on the price of the devices, purchasing procedures and volume of activity of the responding centres was collected on several types of devices used in different centres of the INHS, both for primary total knee replacement and revision knee replacement for 2006 and 2007.

The survey was carried out on a sample of healthcare centres (observational sample) providing primary TKR and revision. From the information contained in the hospital discharge records (SDO) we identified centres that had undertaken at least one total knee replacement or revision procedure (ICD-9-CM 81.54 and 81.55). From this list a proportional stratified sample was extracted by Region and volume of activity. The selection of the centres included in the observation sample was random. We requested information on the models of prosthesis purchased and their product code, name of manufacturers and quantity purchased by single centre; we also asked for information about unit price for single system of prosthesis or unit price for single component of a system and also information on purchase conditions (Directly by Local Unit/Hospitals; Centralised purchase by Regions or other type of organisational level). This was because different purchasing procedures that could influence the purchase price of the device. To complete our data-set, we acquired the volume of activity for the year 2007. We gathered and compared all data.

5.2 Results

5.2.1 Description of sample

Using hospital discharge records we identified 721 centres which had undertaken at least one replacement or revision of the knee in 2006. All the 721 centres were public health centres or private INHS-accredited providers as the hospital discharge records include only public or private accredited centres. We managed data using SAS (The SAS System for Windows – version 8). Random sampling was carried out using the method in Appendix 3. A total of 152 centres were randomly selected and received a structured questionnaire by post and e-mail. Five centres were excluded as they answered that in 2007 they were not accredited by the INHS. The final sample was based on 147 centres. Table 5.1 shows the territorial distribution of the random sample.

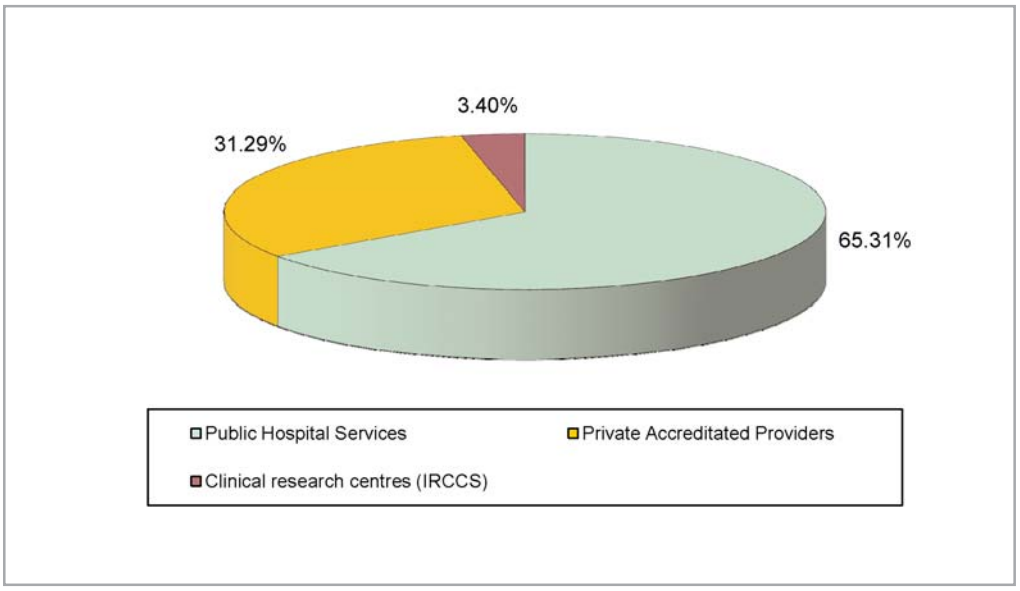
Among the 147 sampled centres, the majority were local hospitals. The percentage of private accredited providers was 31.29%, 3.40% were Clinical Research Centres (IRCCS) and 65.31% were Public Hospital Services (Figure 5.1). In the 721 centres of the INHS, the number of procedures performed for "primary total knee replacement" during 2006 was 49.484 and 2.745 for "revision knee replacement". In the 147 centres sampled the number of procedures performed during 2006 for primary and revision surgery were 12.293 and 699 respectively.

Table 5.1: Regional distribution of the random sample.

Region	Total centres	Sampled centres
Piemonte	44	9
Valle d'Aosta	1	1
Lombardia	113	19
P.A. Bolzano	9	4
P.A. Trento	6	1
Veneto	36	8
Friuli Venezia Giulia	17	4
Liguria	15	4
Emilia Romagna	50	10
Toscana	44	9
Umbria	14	4
Marche	17	5
Lazio	90	13
Abruzzo	25	6
Molise	6	3
Campania	65	11
Puglia	39	8
Basilicata	6	3
Calabria	22	6
Sicilia	80	14
Sardegna	22	5
Total	**721**	**47**

Source: analysis by Agenas on returned questionnaires

Figure 5.1: Type of centres in the random sample (total = 147 centres).



Source: analysis by Agenas on returned questionnaires

5.2.2 Description of responding centres

A total of 66 questionnaires were returned (see Appendix 4). The number of responding centres on the total number of centres sampled within the Italian regions is in Table 5.2. The national percentage of responding centres was 44.9%. In only one region all the selected centres responded. The majority of responding centres were located in northern Italy (53%), 20% were located in central Italy while 27% were located in southern of Italy and the Islands.

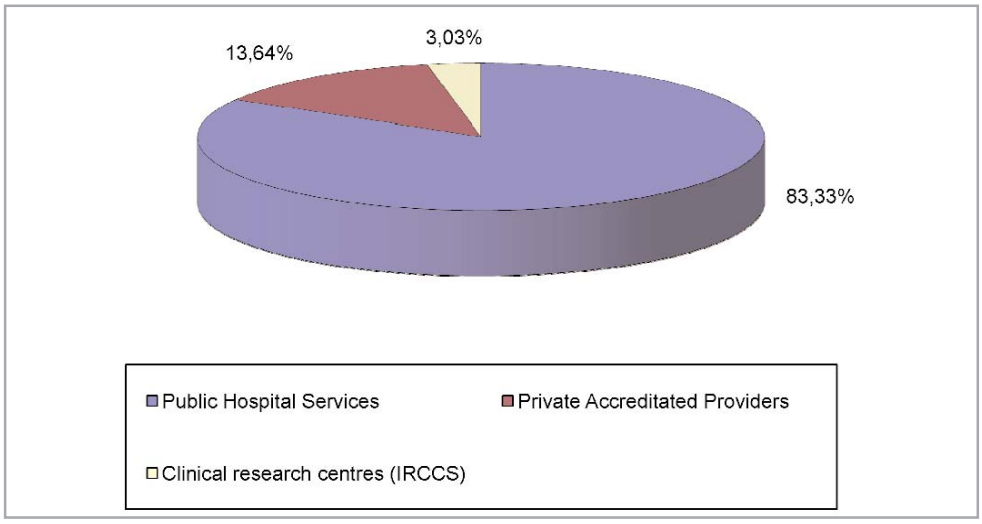
More than 80% of responders were public, 13.3% were private accredited providers (31.3% of the whole sample) (Table 5.2 and Figure 5.2). Three regions did not return questionnaires and no information was collected regarding type of prostheses used, prices and volume of activity.

Table 5.2: Responding centres

Region	Responders	Responding centres/ total regional sample	Responding centres/ total national sample
Piemonte	5	55.56%	7.58%
Valle d'Aosta	0	0.00%	0.00%
Lombardia	11	57.89%	16.67%
P.A. Bolzano	2	50.00%	3.03%
P.A. Trento	0	0.00%	0.00%
Veneto	7	87.50%	10.61%
Friuli Venezia Giulia	0	0.00%	0.00%
Liguria	4	100.00%	6.06%
Emilia Romagna	6	60.00%	9.09%
Toscana	4	44.44%	6.06%
Umbria	1	25.00%	1.52%
Marche	3	60.00%	4.55%
Lazio	5	38.46%	7.58%
Abruzzo	1	16.67%	1.52%
Molise	1	33.33%	1.52%
Campania	5	45.45%	7.58%
Puglia	3	37.50%	4.55%
Basilicata	1	33.33%	1.52%
Calabria	1	16.67%	1.52%
Sicilia	4	28.57%	6.06%
Sardegna	2	40.00%	3.03%
Total	**66**	**44.90%**	**100.00%**

Source: analysis by Agenas on returned questionnaires.
Key: P.A. = Autonomous Province (i.e. regional equivalent)

Figure 5.2: Percentage of responding by type of INHS centres (total = 66 responding centres)



Source: analysis by Agenas on returned questionnaires

5.2.3 Number of procedures performed

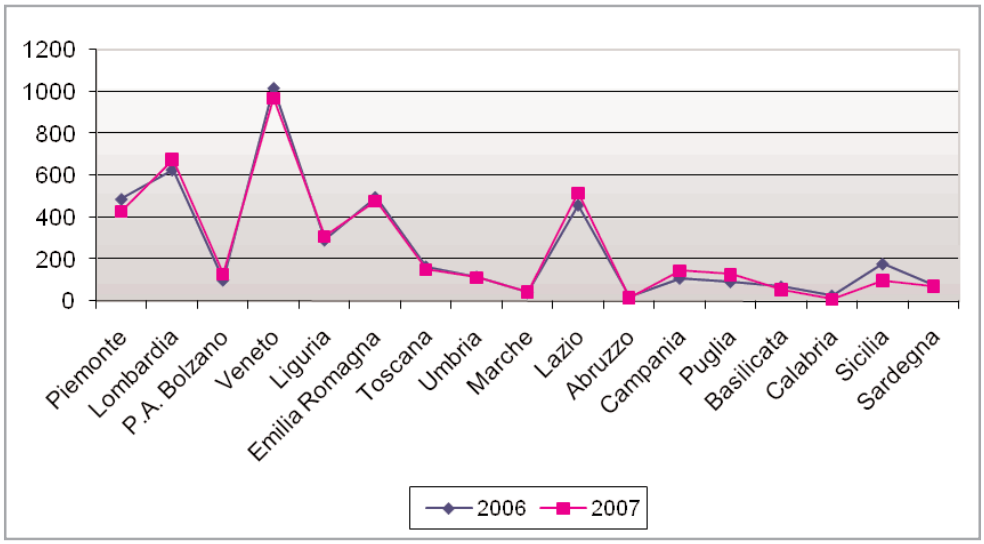
We extracted data on volume of activity for 2006 from hospital discharge records whilst 2007 data came from the questionnaires. The volume of activity within the 66 responding centres was 4.956 procedures during 2006 for total knee replacement (40% of the total of procedures performed by the entire sample of 142 centres). The 2007 volume of activity was incomplete due to a percentage of missing data. Within responding centres the number of procedures performed was 4,345 primary TKRs and 259 revisions. 10 centres omitted data for primary TKR and 20 centres omitted data for revision. Figures 5.3 and 5.4 show the number (by region) of procedures performed by responding centres during 2006-2007. Procedure data are only calculated for the centres for which we had the number of procedures for both 2006 and 2007. There were no substantial differences between 2006 and 2007 in the number of procedures performed for TKR, while revision data show some differences for two Italian regions but the national trend is similar for both 2006 and 2007.

5.2.4 Types of prostheses used

The 66 responding centres purchased 39 different models of knee prosthesis for 2006 and 2007. NEXGEN (ZIMMER) was the most widely used and purchased knee system (more than 800 systems were purchased in 2006 and more than 1,000 in 2007). The list of knee systems, number of providers and relative purchased volume, by responding centres (in 2006 and 2007), are presented in Tables 5.3 and 5.4. There are no substantial differences in terms of utilisation, volume and purchasers, between 2006 and 2007, and no difference between public and private accredited providers.

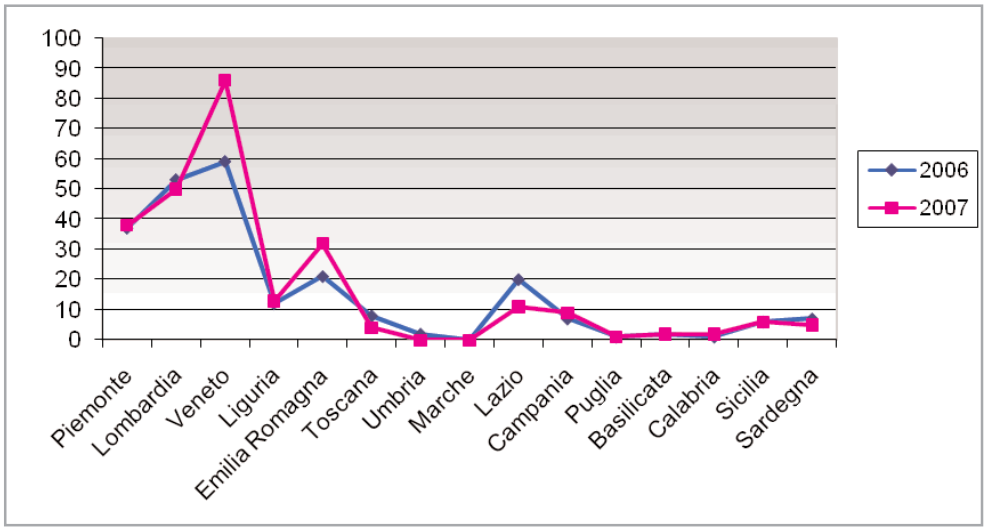
Based on our observations from 66 responding centres it appears that a restricted number of prostheses (NEXGEN, SCORPIO, PROFIX, GENESIS II, LCS, VANGUARD) account for the bulk of the market with NEXGEN being the most purchased and geographically the most popular prosthesis. At the other end of the scale a large number of prostheses are rarely bought and restricted in their geographical spread.

Figure 5.3: Number of total knee replacements by region (56 responding centres)



Source: analysis by Agenas on returned questionnaires

Figure 5.4: Number of revisions by region (46 responding centres)



Source: analysis by Agenas on returned questionnaires

Table 5.3: Volume of purchased prostheses (2006)

Knee System	Hospitals using the system (n = 66)	Volume purchased within the sample
NEXGEN (Zimmer) (ALL MODELS*)	23	> 800
SCORPIO (Stryker)	12	200-299
LCS (DePuy)	11	
PROFIX (Smith & Nephew)	4	
ADVANCE (Wright Medical)	10	100-199
GENESIS II (Smith & Nephew)	10	
P.F.C. SIGMA (DePuy)	9	
SCORE (Amplitude)	7	
VANGUARD (Biomet)	4	
ROTAGLIDE+ (Corin)	3	
INNEX (Zimmer)	4	80-99
MULTIGEN PLUS (Lima)	5	60-79
TC-PLUS (Smith & Nephew)	4	
AGC V2 (Biomet)	2	
GEMINI (Link)	2	
GKS PRIME (Permedica)	2	40-59
OPTETRAK (Exactech)	3	20-39
HLS NOETOS (Tornier)	3	
TRIATHLON (Stryker)	4	
NEXGEN LCCK (Zimmer)	5	
SCORPIO NRG (Stryker)	3	
CONSENSUS (Consensus)	2	
DURACON (Stryker)	3	10-19
3DKNEE SYSTEM (Encore)	1	
ROCC (Biomet)	1	
GKS JUMP (Permedica)	3	< 10
BALANSYS (Mathys)	2	
COLUMBUS (Aesculap)	2	
E.MOTION (Aesculap)	2	
EVOLIS (Medacta)	2	
NATURAL KNEE (Zimmer)	2	
ACADEMIA (F.H. Industrie)	1	
CINETIQUE (Medacta)	1	
ENDOMODEL (Link)	1	
F.I.R.S.T. (Symbios)	1	
JOURNEY (Smith & Nephew)	1	
RT-PLUS (Smith & Nephew)	1	

Source: Agenas on returned questionnaires
(*) All models except NEXGEN LCCK
Note: Manufacturers are reported in Appendix 5.

Table 5.4: Volume of purchased prostheses (2007)

Knee System	Hospitals using the system (n = 66)	Volume purchased within the sample
NEXGEN (Zimmer) (ALL MODELS*)	31	> 1000
SCORPIO (Stryker)	16	400-499
PROFIX (Smith & Nephew)	7	300-399
GENESIS II (Smith & Nephew)	10	200-299
LCS (DePuy)	10	
VANGUARD (Biomet)	6	
SCORE (Amplitude)	9	100-199
P.F.C. SIGMA (DePuy)	7	
TRIATHLON (Stryker)	7	
ADVANCE (Wright)	6	
GEMINI (Link)	5	
TC-PLUS (Smith & Nephew)	5	
GKS PRIME (Permedica)	3	
ROTAGLIDE+ (Corin)	3	
OPTETRAK (Exactech)	5	80-99
INNEX (Zimmer)	3	
SCORPIO NRG (Stryker)	3	60-79
BALANSYS (Mathys)	3	40-59
MULTIGEN PLUS (Lima)	3	
F.I.R.S.T. (Symbios)	2	
RT-PLUS (Smith & Nephew)	1	
NEXGEN LCCK (Zimmer)	7	20-39
AGC V2 (Biomet)	6	
COLUMBUS (Aesculap)	5	
E.MOTION (Aesculap)	3	
CONSENSUS (Consensus)	2	
TRI-CCC (Dedienne Santè)	1	
3DKNEE SYSTEM (Encore)	2	10-19
HLS NOETOS (Tornier)	2	
JOURNEY (Smith & Nephew)	2	
KHEOPS (Transysteme)	2	< 10
ACADEMIA (F.H. Industrie)	1	
DURACON (Stryker)	1	
ENDOMODEL (Link)	1	
EVOLIS (Medacta)	1	
GKS JUMP (Permedica)	1	

Source: Agenas analysis on returned questionnaires
(*) All models except NEXGEN LCCK
Note: Manufacturers are reported in Appendix 5.

5.2.5 Analysis on purchasing price of knee prostheses

The questionnaires provided information about purchasing prices and volumes by knee system and, in some cases, also for single system's components.

On the basis of data from our survey we calculated the mean (weighted) price by the number of models purchased in 2007. From this calculation we obtained a wide price range (€ 2.154,00 to € 5.330,00).

The stratification of all the models of prosthesis according to a single parameter may be very difficult and subjective (see Appendix 1). We decided to privilege the classification based on the biomechanics of the replaced knee. To allow a suitable biomechanical behaviour some different concepts have been applied[18].

We identified 5 classes of prostheses by our survey:

- Multiradius femoral design;
- Single-radius femoral design;
- Medial pivot design;
- Tricondilar femural design;
- Linked, constrained or hinge systems.

Multiradius and single-radius are the most common designs and widely represented on the market. Medial pivot and tricondylar designs are more recent and less represented (only one model for each design).

Linked, constrained or hinge systems present an important mechanical connection between the femoral and the tibial component. Such designs are used when medio-lateral stability is required and are not frequently used in primary TKR.

From this stratification we obtained the range of "mean weighted price" for all prostheses purchased by all centers divided into the 5 classes. Table 5.6 shows that multiradius and single-radius designs have the same mean, minimum and maximum weighted prices. In the multiradius class we took into account the price of €4.680,00 because the maximum value of € 5.016,00 is out of the mean distribution. The other classes have a range that could not be taken into account because of the low representativeness (use) of the model included. All mean weighted prices identified in the survey are reported by model of prosthesis and by femoral class. Tables 5.5 and 5.6 refer only to cemented knee systems.

Table 5.5: List of mean weighted purchase prices by class and model (year 2007).

CLASS	MEAN WEIGHTED PRICE
MULTIRADIUS	
E.MOTION (Aesculap)	€ 5.016,00
VANGUARD (Biomet)	€ 2.862,77
AGC (Biomet)	€ 3.057,80
LCS (DePuy)	€ 3.450,00
P.F.C. SIGMA (DePuy)	€ 3.068,00
MULTIGEN PLUS (Lima)	€ 2.995,00
BALANSYS (Mathys)	€ 2.433,00
EVOLIS (Medacta)	€ 2.500,00
GENESIS II (Smith & Nephew)	€ 2.941,00
GENESIS II OXINIUM (Smith & Nephew)	€ 4.593,57
JOURNEY (Smith & Nephew)	€ 4.680,00
TC-PLUS (Smith & Nephew)	€ 3.407,11
INNEX (Zimmer)	€ 3.142,81
NEXGEN LPS-FLEX (Zimmer)	€ 3.771,00
NEXGEN CR-FLEX (Zimmer)	€ 3.640,00
NEXGEN LPS-FLEX GENDER (Zimmer)	€ 4.280,00
NEXGEN LPS (Zimmer)	€ 2.609,38
SINGLE-RADIUS	
COLUMBUS (Aesculap)	€ 2.404,00
SCORE (Amplitude)	€ 2.839,36
CONSENSUS (Consensus)	€ 2.552,94
3DKNEE SYSTEM (Encore)	€ 3.120,00
GEMINI (Link)	€ 3.288,04
GKS PRIME (Permedica)	€ 2.912,00
PROFIX (Smith & Nephew)	€ 4.609,28
TRIATHLON (Stryker)	€ 2.600,00
SCORPIO (Stryker)	€ 2.508,73
SCORPIO (Stryker)	€ 3.522,74
F.I.R.S.T. (Symbios)	€ 2.812,29
KHEOPS (Transysteme)	€ 2.400,00
MEDIAL PIVOT	
ADVANCE (Wright)	€ 2.154,00
LINKED/CONSTRAINED/HINGE	
ENDOMODEL (Link)	€ 4.100,00
RT-PLUS (Smith & Nephew)	€ 5.330,00
NEXGEN LCCK (Zimmer)	€ 3.355,04
TRICONDILAR	
HLS NOETOS (Tornier)	€ 3.264,29

Source: Agenas analysis on returned questionnaires

Table 5.6: Distribution of mean weighted prices by class.

Class	Number of prosthesis models	Mean weighted price (min)	Mean weighted price (max)
Multiradius	17	€ 2.433,00	€ 5.016,00
Single-radius	12	€ 2.400,00	€ 4.609,28
Linked/Constrained/Hinged	3	€ 3.355,04	€ 5.330,00
Medial Pivot*	1	€ 2.154,00	€ 2.154,00
Tricondilar **	1	€ 3.264,29	€ 3.264,29

Source: Agenas on returned questionnaires
Key:* purchased by one centre only; ** purchased by 2 centres only (range € 3.086,31 to € 3.575,76).

5.3 Stakeholder involvement

All potential stakeholders in previous HTA reports were asked to input into the report's methods. The preparation of this report involved two relevant stakeholders: ASSOBIOMEDICA and ISS. The following manufacturers collaborated to our project: BIOMET, DEPUY, LIMA, LINK, MEDACTA and STRYKER. The ISS also took part in the design and review of the manuscript.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6. Assessing the evidence from clinical studies: systematic review

6.1 Methods

6.1.1 Evidence searches

We conducted a systematic review of the scientific literature in English by consulting the following databases:

- PubMed
- EMBASE
- The Cochrane Library

from 1st January 1998 to 28th February 2009. We used Procite software – ISI ResearchSoft (version 5 Windows 2000/98/95/NT) to manage the bibliography. Details of search strategy and search terms are reported in Appendix 6.

6.1.2 Inclusion criteria

Type of study

We included systematic reviews, randomised controlled trials and observational studies. We also considered HTA reports and guidelines produced in other countries.

Population

We included studies on people older than 50 with OA that received primary total knee replacement (ICD-9-CM 81.54) (assessment of the revision procedure was not a report objective). We also included aggregate data for patients between the ages of 45-49 as long as the observed cases did not exceed 25% of the total.

Type of prostheses

We included studies on prostheses for primary TKR used in Italy by public and private accredited providers as identified by our survey (see chapter 5).

Outcome

The outcome considered was the effectiveness of the devices in terms of implant survival rate.

Follow up

The minimum follow up considered was 5 years.

6.1.3 Evidence synthesis

After the application of the inclusion criteria we extracted data and conducted appraisal of methodological quality in duplicate. Data were extracted from all articles meeting inclusion criteria using a standardised data extraction form used in our previously published HTA reports[23] (Appendix 7). Registry-based studies were extracted using a specific form (Appendix 8). We summarised studies using an evidence table by knee system. Methodological appraisal was conducted using a specific assessment tool developed by Agency for Healthcare Research and Quality (AHRQ)[24] that includes a list of domains to evaluate the quality of single studies (Appendix 9).

6.2 Assessment of outcome: effectiveness of knee prostheses

6.2.1 Effectiveness and safety of knee prostheses: definitions

We considered the effectiveness of knee prostheses used in Italy as the survival of the knee system used in the primary TKR at a minimum period of follow-up of 5 years. The survival rate can be calculated by subtracting 100 from the revision rate. Safety is strictly related to effectiveness.

Revision is understood as the failure of the prosthesis due to a non-traumatic event. The definition of failure in traditional survival statistics is "revision of one or more implant components or removal of the whole prosthesis". Although the indications for revision are known to be sensitive to local conditions, the general consensus appears to favour revision as a blunt endpoint encompassing the main dimensions of outcome. We recognise the magnitude of other indicators of outcome (e.g. pain, range of motion) but implant revision is the only event that can be precisely identified and registered.

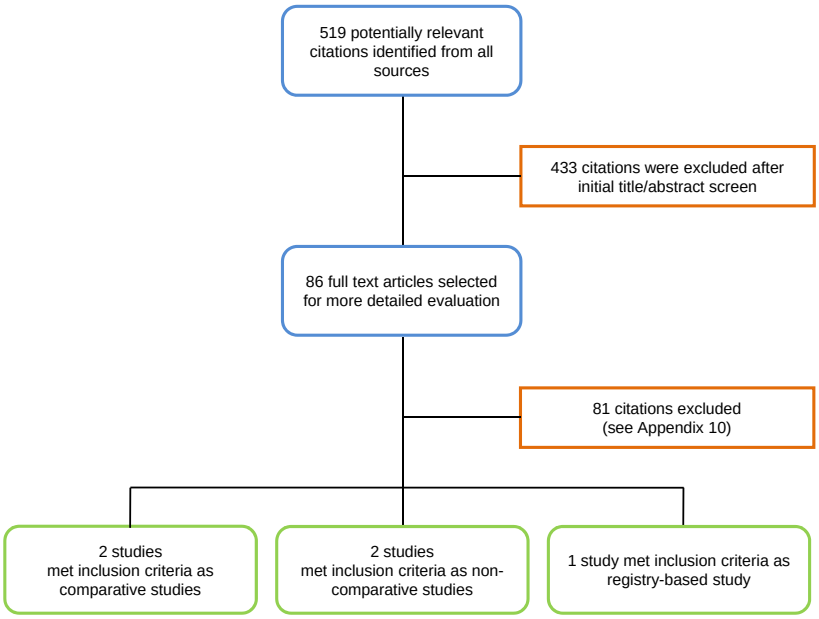
In our analysis we did not consider the effectiveness of the revision procedure (ICD-9-CM 81.55).

6.2.2 Literature results

A total of 519 abstracts were identified in the literature. We excluded 433 citations by reading title and abstract. After this stage we identified 86 potential relevant studies which were retrieved for full text reading. We excluded 81 studies for various reasons after application of inclusion criteria. The list of excluded studies and the reason of exclusion are in Appendix 10.

Finally 5 studies were considered for inclusion in our systematic review. We found no systematic reviews, 1 prospective comparative cohort study[25], 2 randomised controlled studies[26,27], 1 prospective cohort study[28] and 1 registry based study[29]. The list of included studies is in Appendix 11. The evidence flow is in the following flow chart diagram (Figure 6.1).

Figure 6.1: Flow diagram of the inclusion of studies.



6.2.3 Description and quality assessment of included studies

Tables 6.1 and 6.2 summarise the findings of the studies. What follows are brief descriptions

Single studies

Bozic 2005[25] was a comparative prospective cohort study, conducted in USA in a single centre. The study compares two variants of the same knee system: Nexgen cruciate retaining (CR) and Nexgen posterior stabilised (LPS), tested in 287 patients (334 consecutive primary TKR) received either an LPS or CR implant. The main clinical indication for surgery was OA of the knee. The follow up was at 5 and 8 years. Kaplan Mayer (KM) survivorship rates for revision for any reason was 98.7% - 97.5% for Nexgen CR at 5 and 8 year respectively and 100% - 94.6% for Nexgen LPS. The number of implants which underwent revision during the study was 5 for wear, loosening, infections, pain syndrome and fracture. Authors concluded that there were no difference in clinical and radiograph outcomes between two type of prostheses. The general quality of study was good but the setting was not specified, there was an unexplained difference in mortality among groups and generalisability of results was unclear.

Bertin 2005[28] was a prospective cohort study, conducted in the USA in a single centre. The study evaluates the Nexgen CR prosthesis, tested in 198 consecutive patients. The main clinical indication for surgery was OA of the knee. The mean follow up was at 5.9 years (range 5–7 years).

Survival rate as "revision for any reason" was 98.4% at 7 years. Reasons for revisions and number of implants subjected to revision were not reported. The authors concluded that Nexgen CR prosthesis has satisfactory results in terms of performance. The general quality of study was good in terms of study design but evaluation on generalisability of results was unclear.

Beauprè 2007[26] was a multicentric RCT, conducted in Canada. The study compares the same knee system (Scorpio) with different tibial component: uncemented Scorpio HA and cemented Series-7000, were tested in 81 patients randomised in two different groups. The femoral component was uncemented for both groups. The main clinical indication for surgery was non-inflammatory arthritis. The follow up was at 5 years. The revision rates were unclear. Two implants were subjected to revision during the study but the reasons for revision were not reported. Authors concluded that patients reported similar clinical and radiograph outcome at 5 years follow-up although they recognised that this can be considered an intermediate follow-up and future evaluation is required. The general quality of study was good in terms of study design but the generalisability of results was unclear.

McCaskie[27] 1998 was a RCT, conducted in UK. The study compares two types of the same prosthesis with different method of fixation: PFC cemented and PFC uncemented, tested in 114 patients divided in two different groups. The main clinical indication for surgery was OA of the knee. The follow up was at 5 years. No revision occurred at 5 years. Authors concluded that results do not support the use of the more expensive cementless fixation whereas the radiological results are of unknown significance. Longer follow-up was necessary to determine any changes in the results and conclusions. The general quality of study was good in terms of study design and reporting but the generalisability of results was unclear.

Registry-based study

Furnes 2002[29] was a registry-based study. The study evaluated more than 10 prostheses but only 3 of these are used in Italy: AGC (Biomet), Duracon (Stryker), and LCS (DePuy). The study reported cumulative data (not stratified by sex, age and clinical indication of surgery). Survival rate on each prosthesis are presented in Table 6.2. Although the six most used knee systems in Norway showed no statistically significant differences, the authors stated that longer follow-ups are needed to draw conclusions on model, type of fixation, and other characteristics.

6.3. Results of the systematic review

We only included 5 studies in our systematic review and one of these[29] was a registry-based study. The data from the remaining 4 studies[25-28] has limited generalisability as the description of setting and participants were often unclear and the coverage per prosthesis model was low (very few models were assessed). The tiny number of included studies is explained by our decision to search for and include only studies assessing prostheses currently in use in Italy, which had been directly identified by our respondents. It is possible however that other prostheses used in non-responding centres are unknown to us. However, this is unlikely given our consultation with stakeholders and orthopaedic surgeons.

We initially intended to compare revision rates at 5 years for each knee system using performance data from both clinical studies and arthroplasty registers. Due to the lack of high quality studies we decided not to perform this kind of comparison. Although we noted that the knee systems for which we identified clinical studies are among the most used in Italy, we also noted that this number was very low (four models only).

However we recognise that our inclusion criteria were extremely stringent as they are based only on the names of the knee systems used with certainty in Italy, and we excluded groups of patients aged 50 and below and only considered a minimum follow-up of 5-years.

Table 6.1: Evidence table for single studies

Source	Study	Polutation	Device	Follow-up (range) (Y)	Results (survivor rate and/or revision rate)	Authors' conclusions
NEXGEN (ZIMMER)						
Bozic[25] (2005)	Design: Cohort prospective study (comparative) Period: From July 1995 to July 1997 Setting:UC Country: USA Funded by Zimmer Inc.	N° of participants/ N° patients enrolled: 248/287 Group 1: 167 patients (186 knees) had posterior cruciate (CR) retaining TKA Group 2: 120 patients (148 knees) had posterior stabilized (PS) TKA Age at surgery (mean ± SD; (range)) [years]: on 246 patients Group 1: mean age 65.2 Y ± 11.4 (141 pt) Group 2: mean age 65.8 Y ± 10.3 (105 pt) Gender: Group 1: 42 (29.8%) male and 99 female (70.2%) Group 2: 27 male (25.7%) and 78 female (74.3%) Diagnosis (Number of knee): NEXGEN CR: OA 142 ; RA: 8; AVN 4; TA: 1; Other 2. NEXGEN PS: OA 109; RA: 18; AVN 0; TA:2; Other 1.	1) Name of device: Nexgen CR (group 1) Manufacturer: Zimmer (Inc, Warsaw, IN) Class: Multiradius 2) Name: Nexgen LPS (group 2) Manufacturer: Zimmer (Inc, Warsaw, IN) Class: Multiradius	5 - 8 years	KM survivorship rates for revision for any reason: at 5 Y: Group 1: 98.7% [97.4%-100%]; Group 2: 100% [100%] at 8 Y: Group 1: 97.5% [95.00%-100%]; Group 2: 94.6% [89.2%-100%] Survivorship rate for aseptic loosening: at 5 Y: Group 1: 100% [NA]; Group 2: 98.9% [97.8%-100%] Revision for any reason: 3 CR and 2 LPS Wear:[UC] Revised: [1 LPS] Loosening:[U Revised: [1 LPS] Infection (sepsis): [UC] Revised: [1 CR] Pain syndrome: [UC] Revised: [1 CR] Fracture: [UC] Revised: [1 CR] Number of implants subjected to revision during the study: 10 (the information was extracted by study)	"Study found no difference in clinical and/or radiographic outcome between patients with either cruciate-retaining or posterior-stabilized implants"

Bertin[28] (2005)	Design: Choort prospective study Period:From January 1996 and December 1997 Setting: UC Country: USA Funded by Zimmer Inc.	N° of participants/ N° patients enrolled (per group):198/198 consecutive patients (251 knees) Age at surgery (mean ± SD; (range)) [years]: Men: mean age 69 Y (SD 10.22) Women: mean age 69.4Y (SD 10.37) Gender: 77 (39%) males and 121 females (61%) Diagnosis (Number of knee): OA 231; RA 13; ON 3; OPF 3; IA 1.	Name of device: Nexgen CR Manufacturer: (Zimmer Inc., Warsaw, IN) Class: Multiradius	Mean 5.9 years (5-7 years)	Revision rate: - Survival rate for any reason: 98.4% [96.6%-100%] at 7 years - Survival rate for prosthesis-related reason: 100% at 7 years Reason of revision[a]: NR	"The implant used in the study incorporated contemporary design features that provided satisfactory results in a large series of TKAs at 5–7 years follow-up. The implant functioned well in this patient series, and the absence of adverse findings in the radiographic evaluations at 5–7 years follow-up suggested that satisfactory implant function should be maintained. These results warranted ongoing evaluation to confirm the long-term durability and functioning of the implant".
SCORPIO (STRYKER)						
Beaupré[26] (2007)	Design: RCT Period: from Nov 1996 to Aug 2000 Setting: UC (recruitment was made in 3 tertiary healthcare centers in one Canadian region) Country: Canada Funded by Stryker Inc.	N° of participants/ N° patients enrolled (per group):81/81 Group 1: 40 Group 2: 41 Age at surgery (mean ± SD; (range)) [years]: Group 1: mean 63.9 (SD ± 5.8) Group 2: mean 62,9 (SD ± 6.4) Gender: Group 1: 25 female; 15 male Group 2: 25 female; 16 male Diagnosis (Number of knee): NR (inclusion criteria was patients with non-inflammatory arthritis.	1) Name of device: Scorpio with Scorpio HA tibial component (group 1) Manufacturer: Stryker Inc. Class: Single-radius 2) Name of device: Scorpio with Series-7000 tibial component (group 2) Manufacturer: Stryker Inc. Class: Single-radius	5 years	Revision rate on 70 patients: UC Number of implants subjected to revision during the study: Group 1 (1 revision at 3 years); Group 2 (1 revision at 2 years)	"There were no major differences between the two groups over the five-year period. Both fixation methods resulted in good patient-reported, clinical, and gross radiographic outcomes, and no patient underwent revision of the tibial component".

PFC (DEPUY)						
McCaskie[27] (1998)	Design: randomised study Period: Between June 1987 and December 1990 Setting: Hospital Country: UK Funds were received but the funder was not reported	N° of participants/ N° patients enrolled (per group):142/160 (but only 114 patients were assessed at 5 Y) Group 1: 67/114 Group 2: 47/114 Age at surgery (mean ± SD; (range)) [years]: Group 1: 68.8 (±8.2; 41Y- 87Y) Group 2: 70.2 (±7.2; 59Y-86Y) Gender: Group 1: 32 male; 49 female Group 2: 26 male; 32 female Diagnosis (Number of knee): OA Group 1: 84% Group 2: 86%	1) Name of device: PFC cemented Manufacturer: DePuy Class: Multiradius 1) Name of device: PFC uncemented Manufacturer: DePuy Class: Multiradius	5 years	Revision in 114 patients and 139 prostheses: 0	"At five years, our clinical results do not support the use of the more expensive cementless fixation whereas the radiological results are of unknown significance. Longer follow-up will determine any changes in the results and conclusions. We are currently awaiting the results of the ten-year assessments, after which we will present a more extensive survival analysis".

a) Complication: Wear; Loosening; Dislocation; Infection; Osteolysis; Other.
Key: UC = unclear; TKA = total knee arthroplasty; Y = years; pt = patients; OA = osteoarthritis; RA = rheumatoid arthritis; AVN = avascular necrosis; TA = traumatic arthritis; KM = Kaplan-Meier; ON = osteonecrosis; OPF = osteoarthritis with posttraumatic fracture; IA = inflammatory arthritis.

Table 6.2: Summary of the registry-based study (Furnes 2002)[29]

Knee system	Total	Number of revisions	Survival rate at 5 years (95% CI)
Tricompartimental (patella resurfaced)			
AGC (Biomet)	279	4	97.4 (94.7-100)
DURACON (Stryker)	101	1	98.6 (95.7-100)
LCS (DePuy)	281	6	NR
Bicompartimental (not patella resurfaced)			
AGC (Biomet)	687	16	96.5 (94.8-98.3)
DURACON (Stryker)	188	6	NR
LCS (DePuy)	476	4	97.2 (93.5-100)

Note: Data were collected from 59 Hospitals in Norway from January 1999 to May 2000.
The mean age of all 7,174 patients was 70 years, 74% were women.
Key: NR = Not reported; CI = Confidence Interval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7. Assessing the evidence from arthroplasty registers

7.1 Introduction to arthroplasty registers

Arthroplasty registers are usually managed by orthopaedic associations or government institutions. Registers collect information on primary and revision procedures performed in a defined geographical area, usually a single country. However, some regional registers also exist. Registers reflect the standards in surgical procedures of their health system. Hip and knee prostheses registers are quite common, but recently because of the increasing number of procedures, data on shoulder, elbow, ankle, and vertebral prostheses have also been collected[30,31].

Each country uses their register data to assess prostheses performance since they can provide acceptable general and cumulative estimates. However, since each national register is an integral part of its health system, its data may have a highly context-specific profile. Differences between countries, such as experience in cementing techniques, availability of implant designs, surgical approaches used, regimes of rehabilitation, or general organisational and cultural features of the health system, may affect the outcome of the intervention[32].

Registries commonly release periodic reports for disseminating findings and results. The reports are often open-access and downloadable free of charge from the homepage of the Registry. Dissemination is also achieved by publishing specific studies or reports in specialised peer-reviewed journals.

In Europe, several arthroplasty registers are included in the European Arthroplasty Register (EAR). EAR is a project of the European Federation of National Associations of Orthopaedics and Traumatology (EFORT). EFORT is a not-for-profit organisation[33].

EAR works as a voluntary cooperation of independent national arthroplasty registers. Among the main aims of EAR there are the following[34]:

- definition of common standards for data collection, data management and evaluation at European level to assure a high level of comparability of national register data;
- development of register documentation and standardisation at the highest level;
- registration of larger number of different implants in higher number of cases than possible in single national registers;
- comparison of different countries and different health systems concerning rate of revision;
- support for national orthopaedic societies in development of national arthroplasty registers.

In our assessment of prostheses for TKR, we wanted to use data from knee registers since the data are more likely to be generalisable than data from formal studies with selected populations (i.e. they have a higher likelihood that the types of patients, indications and procedures reflect real everyday practice). In addition, register denominators are also likely to be more numerous and with a longer follow-up than data from formal studies (i.e. clinical trials). Thus we assumed that such data could successfully be used to enhance the evidence from formal studies (see

chapter 6 for the systematic review of the evidence from formal studies). In particular, our aim was to collect, for each prosthesis model (identified by model name and manufacturer), performance estimates at 5 (and possibly 10) years' follow-up.

7.2 Methods for the identification and analysis of the knee registers

We identified knee registers accessing the EFORT portal with related web-links[35]. For each register, we downloaded the last available periodic report.

We were interested in collecting performance data for each knee system, i.e. revision (or survival) rate expressed as a percentage at a set follow-up period, reported in one or more registers. We performed a systematic comparison of the indicators of performance presented in the periodic reports.

To compare data from registers with data from clinical studies, we took into account the detail of reporting of the population receiving the prosthesis. In particular, as the patient age was one of the inclusion criteria of our systematic review, we decided to consider this variable to stratify performance data for each specific implant model. We looked at each register's last published periodic report for the data we needed and, when these were not reported, or when they were presented in an unsuitable format for our analysis, we corresponded with a key-person (e.g. the register's coordinator) asking for additional data.

7.3 Results

By accessing the EFORT website we obtained 9 periodic reports: 6 from European countries and 3 from non-European countries (Table 7.1). By contacting key-persons we also became aware of other national registers (e.g., Austria, Czech Republic, France, Hungary, Italy, Slovak Republic, and Switzerland). However these registers are in their early implementation phases and no periodic reports were available for our analysis. We also intended to consider data from the Italian regional arthroplasty registers (Table 7.1). Two out of 21 regions (Emilia-Romagna and Lombardia) are currently using a register for knee implants.

7.3.1 Comparison of format and content

Among the 9 periodic reports of national registers identified (Table 7.1), none presented the data in the format we needed. From our comparison of the indicators of performance we noted that considerable heterogeneity in data reporting existed. The more important finding is that data referring to the implant survival, recognised by EAR/EFORT as one of the most important variables and included within the main aims of an arthroplasty register (see EFORT website[33]), were often missing in the periodic reports or were reported only in cumulative form (e.g., per method of fixation, per age group).

Only four reports out of the 9 reported performance data by implant model: Australia, England and Wales, New Zealand, and Sweden. Among the 2 periodic reports of Italian regional registers identified, only the report from the Emilia-Romagna region reported performance data by prosthesis model. This left 5 reports suitable for in-depth analysis. The findings of this preliminary examination are synthesised in Table 7.2.

Even within the 5 reports considered for our further analysis (Australia, Emilia-Romagna, England and Wales, New Zealand, and Sweden) performance data were reported in different ways. Only the reports from Australia and New Zealand presented performance data in a homogeneous format that could be compared without additional manipulation or transformation. Emilia-Romagna, England and Wales, and Sweden presented performance data as reported in Table 7.3.

Table 7.1: Knee registers identified (in alphabetical order). For each register we downloaded the last updated periodic report.

Country	Year of the last updated report	Language of the report	Web link
Australia	2008	English	http://www.dmac.adelaide.edu.au/aoanjrr/index.jsp
Canada	2007	English	http://secure.cihi.ca/cihiweb/dispPage.jsp?cw_page=services_cjrr_e
Denmark	2007	Danish	http://www.dshk.org/DKR-frame.htm
England and Wales	2006	English	http://www.njrcentre.org.uk/njrcentre/default.aspx
Finland	2006	English	http://www.nam.fi/publications
New Zealand	2007	English	http://www.cdhb.govt.nz/NJR/
Norway	2008	English	http://www.haukeland.no/nrl/eng/default.htm
Scotland	2008	English	http://www.arthro.scot.nhs.uk/index.htm
Sweden	2008	English	http://www.knee.nko.se/english/online/thePages/index.php
Italian Regions			
Emilia-Romagna	2007	Italian	https://ripo.cineca.it/
Lombardia	2008	Italian	www.sanita.regione.lombardia.it/pubblicazionivarie/rapporto_registro_ortopedico.htm

Table 7.2: Results of the preliminary examination of the registers' reports identified. We focused on the reporting related to the implants' performance.

Country of the register	Implant performance by model	Notes
Australia	YES	Considered for further analysis
Canada	NO	Performance data were cumulative for all the procedures
Denmark	NO	Performance data were by femoral components only
England and Wales	YES	Considered for further analysis
Finland	NO	Does not report performance data
New Zealand	YES	Considered for further analysis
Norway	NO	Does not report performance data
Scotland	NO	Performance data cumulative for all the procedures
Sweden	YES	Considered for further analysis
Italian Regions		
Emilia-Romagna	YES	Considered for further analysis
Lombardia	NO	Does not report performance data

Cumulative measures of performance, such as revision or survival rate, revision rate per 100 component-years, yearly cumulative percent of revision (CPR), and risk of revision (RR), report the general performance of each knee system.

We found the following problems:

- the population receiving the implant was either not stratified into sub groups or stratified in different ways across registers;
- four different prosthesis-related outcomes were reported in five reports (revision rate, survival rate, revision rate per 100 component-years, and risk of revision);
- the follow-up reporting intervals were 1, 3, 5, 6, and 7 years;
- age groups overlapped.

Heterogeneity of reporting causes major data loss, by hampering meaningful comparisons between registers. As all Registries identified are linked by EAR/EFORT, we expected a higher degree of homogeneity.

Table 7.3: Variables used in each register to report implant performance.

Country of the register	Data on implant performance presented in cumulative form	Data on implant performance presented by implant model
Australia	Revision rate per 100 component-years and yearly cumulative percent revision stratified by: - age groups (<55, 55-64, 65-74, >75) - gender (F/M) - bearing mobility (fixed, rotating, sliding, rotating-sliding) - stability (minimal, posterior stabilised, fully stabilised, hinged) - patella usage - fixation (cemented, uncemented, hybrid)	- Revision rate per 100 component-years - Yearly cumulative percent revision - Follow-up at 1, 2, 3, 5, and 7 years - Cut-off at 300 implants
Emilia-Romagna	Number of revision stratified by: - bearing mobility (fixed, mobile)	- Survival rate at 6 years - Patients with age <70 years - Cut-off at 100 implants
England and Wales	Revision rate at 1 year of follow-up stratified by: - age groups (<65, 65-74, >75) - gender (F/M) - patient physical status - fixation (cemented, uncemented) - provider type (type of hospital) - use of mini-invasive surgery	- Revision rate for the 5 most used knee systems - Kaplan-Meier curves for the 5 most used knee systems - Follow-up at 1 and 3 years
New Zealand	Revision rate per 100 component years stratified by: - fixation (cemented, uncemented, hybrid) - age groups (<55, 55-64, 65-74, >74) - surgical approach (medial, lateral, other) - ASA class - type of hospital (public, private) - surgeon annual workload (<10, 10-25, 25-50, 50-75, 75-100 procedures)	- Revision rate per 100 component years - Cut-off at 200 implants
Sweden	Cumulative revision rate stratified by: - region - indication (OA, rheumatoid arthritis) - age groups (<64, 65-74, >75) - gender (F/M) - year of operation - type of implant (total, linked, hinges) - fixation (hybrid, no cement, all cemented) - usage of patella	- Risk of revision - Kaplan-Meier curves for cumulative revision rate - Cut-off at 160 implants

Key: ASA = American Society of Anaesthesiologists; OA=osteoarthritis

Since the characteristics of patients receiving a prosthesis are unlikely to be homogeneous, the stratification of performance data per group of patients is important to allow comparisons across registers. For example, gender, age, and indication for procedure should be reported. As stated in our previous HTA report on the prostheses for total hip replacement [23] we believe that, the performance of each knee system (clearly identified by system name and manufacturer) should be expressed with stratification by sex, age groups and indication, to allow a more efficient analysis. All these variables affect the implant-related outcome[36,37].

We attempted to overcome heterogeneity of data to compare data-sets from each register. We corresponded with key persons from the 11 registers identified (reported in Table 7.1) to obtain further data related to the last published report. Data requests were made by e-mail, introducing the Agenas and explaining the HTA report's objectives. The recipients were informed that the project was commissioned and financed by the Italian MLHSP. Results are shown in the next paragraph.

7.3.2 Implants performance from arthroplasty registers

Replies obtained from our data requests were various and are synthesised in Table 7.4. We received all data requested from 3 out of the 11 registers contacted: Australia, Emilia-Romagna, and New Zealand. We further asked for additional stratification by age (patients aged 50 and over). Only Australia and Emilia-Romagna sent us the additional data and thus we were forced to exclude the New Zealand register because of the absence of sufficient age breakdown. This reduced our sources to 2 registers.

From the data obtained we were able to collect, for each implant model, the following variables:

- Implant name (model name and manufacturer);
- Total number of procedures performed with the implant;
- Percent of females and males who received the implant;
- Mean age (and range) of the population that received the implant;
- Percent of procedures performed for OA;
- Revision rate at 3 and 5 years of follow-up.

These data are presented for Australia (Tables 7.5-7.7), Emilia-Romagna (Table 7.8), and New Zealand (Table 7.9 and 7.10) respectively.

TKR appeared most commonly performed in females than in males and the rate of OA as primary indication appeared to be around 90% (this seems verified in all three registers except in Emilia-Romagna where this seems slightly lower). The mean age for primary TKR was over 60 years for all the three registers. Moreover, the 10 most used knee systems cover more than 70% of the total number of observations in each register and several of these seem to be among the most frequently used implants in all the registers (for cemented, uncemented and hybrid fixation).

Table 7.4: Replies from the key-persons contacted to request further information on the performance of knee implants.

Register	Reply
A	"All the data you have mentioned (apart from BMI which the Registry does not collect) is available… If there is any further information you require please let us know."
B	"Unfortunately, we work with a voluntarily registration for surgeons who perform hip and knee replacement, i.e. we do not track individual patient over time. We are unable to provide you the information you need (survival rate)."
C	"I am sorry but we cannot help you with the analyses that you want. We do not register the data you are asking for on a regular basis."
D	"I am pleased to enclose a data request form…" [with a request for payment]
E	"I'm sorry to inform you that we don't have any possibilities to send the data to you. Our office is under new organisational reform."
F	"We can provide data for gender, age and diagnosis, but not BMI. We would be pleased to collaborate with you in your project."
G	"We are sorry to inform you that we will not be able to help you with your enquiry. It is our policy not to publish reports on prosthesis performance unless it is in a setting using appropriate statistical methods for adjustment for possible confounders, together with a thorough discussion of the results. We publish the prostheses results in peer reviewed journals to quality control our publications."
H	No reply
I	"The only information available is that which can be found in our annual reports and scientific articles."
J	"We can provide all the data you asked for."
K	"We cannot help you. The data you are asking for are not available yet."

Note: The co-ordinator of one register was available for collaboration and sharing of data but, since the register started to collect data for knee implants in 2007, no analyses were available due to the short period of the time.

Table 7.5: Data from the Australian Orthopaedic Association National Joint Replacement Register (AOAJRR) showing revision rates at 3 and 5 years by variables of the receiving population. This table refers to cemented fixation only.

Knee system (cemented)	Total obs.	Female/Male [%]	Mean age (range)	OA [%]	3 years (95% CI)	5 year (95% CI)
GENESIS II (SMITH & NEPHEW)	9,827	60/40	72 (-)	96.3	2.7 (2.4; 3.2)	3.5 (3.0; 4.0)
P.F.C. SIGMA (DEPUY)	8,984	60/40	70 (-)	96.2	2.0 (1.6; 2.3)	2.8 (2.3; 3.4)
DURACON (STRYKER)	8,183	61/39	71 (-)	95.9	2.4 (2.1; 2.8)	3.2 (2.8; 3.7)
NEXGEN CR (ZIMMER)	7,152	66/34	70 (-)	96.1	1.3 (1.0; 1.7)	1.7 (1.3; 2.2)
NEXGEN LPS FLEX (ZIMMER)	6,608	51/49	69 (-)	97.1	2.6 (2.2; 3.2)	3.3 (2.6; 4.2)
GENESIS II OXINIUM (SMITH & NEPHEW)	6,280	54/46	65 (-)	97.7	3.0 (2.5; 3.6)	5.1 (4.0; 6.4)
SCORPIO (STRYKER)	5,146	63/37	71 (-)	95.2	2.8 (2.3; 3.4)	3.7 (3.0; 4.4)
LCS (DEPUY)	4,110	60/40	70 (-)	95.1	3.7 (3.1; 4.3)	4.9 (4.2; 5.6)
NEXGEN LPS (ZIMMER)	3,808	57/43	70 (-)	96.6	2.1 (1.7; 2.7)	2.8 (2.3; 3.5)
PROFIX (SMITH & NEPHEW)	3,512	58/42	69 (-)	96.5	3.4 (2.7; 4.1)	4.0 (3.3; 4.8)
AGC (BIOMET)	2,679	58/42	70 (-)	97.1	2.2 (1.7; 2.9)	3.0 (2.3; 3.9)
TRIATHLON (STRYKER)	2,269	63/37	69 (-)	96.6	- (-; -)	- (-; -)
KINEMAX PLUS (STRYKER)	1,681	56/44	70 (-)	97.7	2.3 (1.7; 3.2)	2.9 (2.1; 3.9)
NATURAL KNEE (ZIMMER)	1,167	71/29	73 (-)	94.4	1.5 (0.9; 2.5)	1.9 (1.1; 3.0)
OPTETRAK-PS (EXACTECH)	996	55/45	69 (-)	97.2	5.7 (4.2; 7.9)	6.9 (4.9; 9.5)
RBK SYSTEM (G.M.T.)	621	68/32	70 (-)	96.6	3.0 (1.6; 5.6)	3.0 (1.6; 5.6)
MAXIM (BIOMET)	552	68/32	70 (-)	95.8	2.8 (1.7; 4.8)	4.5 (2.8; 7.1)
ADVANCE (WRIGHT)	531	55/45	70 (-)	97.0	5.9 (4.1; 8.4)	6.5 (4.5; 9.2)
JOURNEY (SMITH & NEPHEW)	460	58/43	67 (-)	97.0	- (-; -)	- (-; -)
ZIMMER MBK (ZIMMER)	296	63/37	68 (-)	95.3	2.7 (1.4; 5.4)	4.9 (2.9; 8.1)
BALANSYS (MATHYS)	230	50/50	71 (-)	95.2	2.8 (1.2; 6.7)	3.7 (1.7; 8.3)
ACTIVE KNEE (ASDM)	207	72/28	74 (-)	93.7	4.0 (1.9; 8.4)	- (-; -)
I/B II (ZIMMER)	199	46/54	71 (-)	99.0	3.0 (1.4; 6.7)	6.8 (4.0; 11.4)
APOLLO (ZIMMER)	168	69/31	71 (-)	95.8	0.6 (0.1; 4.2)	0.6 (0.1; 4.2)
NEXGEN LCCK (ZIMMER)	122	69/31	70 (-)	83.6	- (-; -)	- (-; -)
ADVANTIM (WRIGHT)	118	60/40	73 (-)	95.8	0.8 (0.1; 5.9)	0.8 (0.1; 5.9)
ROCC (BIOMET)	117	59/41	70 (-)	96.6	- (-; -)	- (-; -)
GENESIS (SMITH & NEPHEW)	112	64/36	72 (-)	99.1	5.7 (2.6; 12.2)	6.7 (3.3; 13.6)
VKS (SMITH & NEPHEW)	110	52/48	71 (-)	98.2	- (-; -)	- (-; -)
ROTAGLIDE+ (CORIN)	97	45/55	72 (-)	95.9	2.1 (0.5; 8.2)	- (-; -)
OPTETRAK-CR (EXACTECH)	85	60/40	70 (-)	95.3	6.8 (2.9; 15.7)	- (-; -)
OXFORD TMK (BIOMET)	75	55/45	62 (-)	94.7	1.3 (0.2; 9.1)	1.3 (0.2; 9.1)
SERIES 7000 (STRYKER)	67	40/60	76 (-)	98.5	1.5 (0.2; 10.3)	1.5 (0.2; 10.3)
AMK (DEPUY)	58	72/28	70 (-)	93.1	7.0 (2.7; 17.6)	12.3 (6.1; 24.1)
S-ROM (DEPUY)	56	55/45	68 (-)	60.7	- (-; -)	- (-; -)

Key: obs. = observations; CI = confidence interval; - = not reported; G.M.T. = Global Manufacturing Technology; ASDM = Advanced Surgical Design & Manufacture; OA = osteoarthritis.
Note: Missing revision rates were marked with "- (-; -)". This means that estimates at follow-up can not be calculated yet (e.g. the number of observations was too low for survival analysis or the follow-up did not reach 3 years).

Table 7.6: Data from the Australian Orthopaedic Association National Joint Replacement Register (AOAJRR) showing revision rates at 3 and 5 years by variables of the receiving population. This table refers to uncemented fixation only.

Knee system (uncemented)	Total obs.	Female/Male [%]	Mean age (range)	OA [%]	3 years (95% CI)	5 years (95% CI)
NEXGEN (ZIMMER)	5,874	53/47	69 (-)	97.3	2.0 (1.6; 2.4)	2.1 (1.7; 2.6)
SCORPIO (STRYKER)	3,351	56/46	69 (-)	97.9	3.1 (2.5; 3.9)	4.1 (3.3; 5.2)
DURACON (BIOMET)	2,948	52/48	69 (-)	97.2	2.7 (2.1; 3.4)	3.4 (2.7; 4.4)
ACTIVE KNEE (ASDM)	2,477	46/54	65 (-)	98.4	3.2 (2.5; 4.1)	4.1 (3.2; 5.3)
LCS (DEPUY)	2,309	55/45	68 (-)	97.3	3.3 (2.6; 4.1)	4.1 (3.3; 5.0)
RBK SYSTEM (G.M.T.)	1,971	54/46	68 (-)	98.7	2.6 (1.9; 3.6)	3.0 (2.1; 4.1)
NATURAL KNEE (ZIMMER)	1,685	51/49	68 (-)	98.2	2.3 (1.7; 3.2)	3.4 (2.6; 4.6)
PROFIX (SMITH & NEPHEW)	921	51/49	69 (-)	96.4	2.9 (1.9; 4.4)	3.6 (2.3; 5.5)
TRIATHLON (STRYKER)	752	44/56	67 (-)	98.7	- (-; -)	- (-; -)
ADVANTIM (WRIGHT)	583	60/40	67 (-)	97.6	1.6 (0.7; 3.3)	1.6 (0.7; 3.3)
MAXIM (BIOMET)	576	55/45	69 (-)	97.4	3.2 (2.0; 5.0)	3.4 (2.2; 5.3)
NATURAL KNEE II (ZIMMER)	399	44/56	68 (-)	98.2	- (-; -)	- (-; -)
ROTAGLIDE+ (CORIN)	347	49/51	68 (-)	97.7	3.2 (1.7; 6.0)	4.1 (2.3; 7.3)
ADVANCE (WRIGHT)	292	57/43	70 (-)	98.3	3.7 (2.0; 6.7)	4.8 (2.7; 8.3)
ROCC (BIOMET)	218	54/46	69 (-)	98.2	- (-; -)	- (-; -)
NEXGEN LPS (ZIMMER)	193	53/47	67 (-)	97.4	- (-; -)	- (-; -)
COLUMBUS (AESCULAP)	133	46/54	69 (-)	100	- (-; -)	- (-; -)
GENESIS II (SMITH & NEPHEW)	111	49/61	64 (-)	98.2	- (-; -)	- (-; -)
BUECHEL-PAPPAS (ENDOTEC)	69	45/55	69 (-)	97.1	- (-; -)	- (-; -)
PROFIX OXINIUM (SMITH & NEPHEW)	53	58/42	63 (-)	96.2	- (-; -)	- (-; -)
INTERAX (STRYKER)	51	43/57	72 (-)	92.2	2.0 (0.3; 13.6)	8.5 (3.3; 21.1)

Key: obs. = observations; CI = confidence interval; ASDM = Advanced Surgical Design & Manufacture; G.M.T. = Global Manufacturing Technology; OA = osteoarthritis.
Note: Missing revision rates were marked with "- (-; -)". This means that estimates at follow-up can not be calculated yet (e.g. the number of observations was too low for survival analysis or the follow-up did not reach 3 years).

Table 7.7: Data from the Australian Orthopaedic Association National Joint Replacement Register (AOAJRR) showing revision rates at 3 and 5 years by variables of the receiving population. This table refers to hybrid fixation only.

Knee system (hybrid)	Total obs.	Female/Male [%]	Mean age (range)	OA [%]	3 years (95% CI)	5 years (95% CI)
DURACON (STRYKER)	6,901	58/42	70	97.3	2.6 (2.2; 3.0)	3.3 (2.9; 3.9)
SCORPIO (STRYKER)	6,470	57/43	69	97.7	2.4 (2.0; 2.9)	3.6 (3.0; 4.3)
NEXGEN (ZIMMER)	5,410	56/44	69	97.3	1.6 (1.3; 2.1)	2.3 (1.7; 2.9)
P.F.C. SIGMA (DEPUY)	4,840	59/41	70	98.4	2.7 (2.3; 3.3)	3.7 (3.1; 4.4)
GENESIS II (SMITH & NEPHEW)	3,096	57/43	69	98.5	3.1 (2.5; 3.9)	3.6 (2.9; 4.5)
LCS (DEPUY)	2,165	56/44	70	96.1	2.5 (1.9; 3.2)	3.7 (3.0; 4.7)
MAXIM (BIOMET)	1,285	56/44	69	97.7	2.4 (1.6; 3.6)	3.2 (2.2; 4.7)
AGC (BIOMET)	1,118	58/42	73	97.9	1.4 (0.8; 2.4)	2.2 (1.3; 3.5)
NATURAL KNEE (ZIMMER)	1,097	58/42	69	97.6	1.8 (1.2; 2.8)	2.3 (1.5; 3.6)
ACTIVE KNEE (ASDM)	805	66/34	71	96.1	2.9 (1.7; 5.0)	- (-; -)
PROFIX (SMITH & NEPHEW)	693	59/41	69	97.7	3.1 (2.0; 4.9)	4.0 (2.6; 6.1)
NEXGEN LPS (ZIMMER)	623	58/42	69	98.1	1.4 (0.6; 3.3)	4.8 (2.5; 9.0)
TRIATHLON (STRYKER)	522	61/39	70	98.3	- (-; -)	- (-; -)
ADVANCE (WRIGHT)	283	73/27	72	97.2	2.4 (1.1; 5.3)	- (-; -)
RBK SYSTEM (G.M.T.)	272	63/37	68	97.8	1.7 (0.6; 5.3)	- (-; -)
OPTETRAK-CR (EXACTECH)	229	55/45	69	97.8	2.6 (1.1; 6.2)	3.3 (1.5; 7.1)
NEXGEN LPS FLEX (ZIMMER)	191	54/46	68	99	- (-; -)	- (-; -)
ZIMMER MBK (ZIMMER)	179	46/54	65	96.1	1.7 (0.5; 5.2)	2.4 (0.9; 6.2)
ROTAGLIDE+ (CORIN)	172	60/40	69	97.7	6.9 (3.9; 12.1)	- (-; -)
GENESIS II OXINIUM (SMITH & NEPHEW)	149	52/48	64	94.6	21.4 (15.1; 29.7)	- (-; -)
AMK (DEPUY)	144	60/40	72	96.5	4.2 (1.9; 9.2)	4.2 (1.9; 9.2)
OPTETRAK-PS (EXACTECH)	136	62/38	70	99.3	6.1 (2.8; 13.2)	6.1 (2.8; 13.2)
APOLLO (ZIMMER)	114	42/58	68	99.1	0.9 (0.1; 6.1)	0.9 (0.1; 6.1)
TRAC (BIOMET)	90	57/43	68	98.9	4.4 (1.7; 11.4)	8.1 (3.9; 16.3)
TC-PLUS (SMITH & NEPHEW)	60	60/40	72	96.7	- (-; -)	- (-; -)
VKS (SMITH & NEPHEW)	59	66/34	72	94.9	- (-; -)	- (-; -)
ADVANTIM (WRIGHT)	53	94/6	73	94.3	- (-; -)	- (-; -)
ROCC (BIOMET)	51	51/49	69	100	- (-; -)	- (-; -)

Key: obs. = observations; CI = confidence interval; ASDM = Advanced Surgical Design & Manufacture; G.M.T. = Global Manufacturing Technology; OA = osteoarthritis.
Note: Missing revision rates were marked with "- (-; -)". This means that estimates at follow-up can not be calculated yet (e.g. the number of observations was too low for survival analysis or the follow-up did not reach 3 years).

Table 7.8: Data from Registro dell'Implantologia Protesica Ortopedica (RIPO, Register of the Orthopaedic Prosthetic Implants) of Emilia-Romagna showing revision rates at 3 and 5 years by variables of the receiving population. This table refers to all fixation methods (cemented, uncemented, hybrid). However, more than 85% of procedures collected in the RIPO were performed using cemented fixation.

Knee system (all methods of fixation)	Total obs.	Female/Male [%]	Mean age (range)	OA [%]	3 years (95% CI)	5 years (95% CI)
NEXGEN[a] (ZIMMER)	6,193	76/24	71 (18-92)	88.6	1.9 (1.4; 2.3)	2.1 (1.6; 2.6)
PROFIX (SMITH & NEPHEW)	3,748	75/25	71 (35-91)	89.4	2.1 (1.6; 2.7)	2.4 (1.7; 3.0)
P.F.C. SIGMA (DEPUY)	1,928	77/23	70 (26-92)	82.0	2.7 (1.9; 3.6)	3.2 (2.1; 4.2)
SCORPIO (STRYKER)	1,490	70/30	71 (24-87)	89.4	2.0 (1.0; 3.0)	2.0 (1.0; 3.0)
GENESIS II (SMITH & NEPHEW)	925	74/26	71 (24-87)	88.5	1.5 (0.3; 2.7)	- (-; -)
INTERAX (STRYKER)	732	74/26	72 (47-94)	92.1	3.9 (2.4; 5.3)	5.4 (3.4; 7.3)
GEMINI (LINK)	650	77/23	73 (39-93)	89.5	1.1 (0.0; 2.3)	- (-; -)
LCS (DEPUY)	637	71/29	74 (49-87)	88.5	2.0 (0.7; 3.2)	2.5 (0.9; 4.0)
T.A.C.K. (LINK)	631	74/26	71 (28-86)	95.2	4.1 (2.5; 5.7)	5.6 (3.7; 7.6)
OPTETRAK (EXACTECH)	592	75/25	72 (36-86)	80.1	2.2 (0.5; 2.8)	2.7 (0.8; 4.6)
ADVANCE (WRIGHT)	547	75/25	73 (38-90)	93.2	3.0 (1.3; 4.8)	3.8 (1.5; 6.1)
ROTAGLIDE+ (CORIN)	498	70/30	72 (30-88)	87.6	4.9 (2.8; 7.1)	5.5 (3.1; 7.8)
AGC (BIOMET)	493	74/26	72 (36-87)	91.3	- (-; -)	- (-; -)
TRI-CCC (DEDIENNE SANTÉ)	448	77/23	74 (55-89)	96.4	3.4 (1.6; 5.3)	5.4 (2.5; 8.3)
TC-PLUS (SMITH & NEPHEW)	447	74/26	72 (44-87)	80.7	- (-; -)	- (-; -)
SCORE (AMPLITUDE)	428	77/23	73 (47-92)	90.2	- (-; -)	- (-; -)
MULTIGEN PLUS (LIMA)	360	84/16	72 (24-88)	94.7	4.8 (0.1; 9.5)	- (-; -)
913 (WRIGHT)	357	73/27	71 (41-90)	83.5	0.9 (0.0; 1.8)	1.3 (0.1; 2.5)
VANGUARD (BIOMET)	341	71/29	68 (37-87)	89.1	- (-; -)	- (-; -)
PERFORMANCE (BIOMET)	277	72/28	70 (21-85)	86.6	2.6 (0.7; 4.5)	3.2 (1.0; 5.5)
HLS EVOLUTION (TORNIER)	269	75/25	70 (23-90)	76.6	0.8 (0.0; 2.0)	0.8 (0.0; 2.0)
G.K.S. (PERMEDICA)	259	65/35	73 (47-89)	96.5	2.1 (0.0; 4.1)	- (-; -)
DURACON (STRYKER)	258	74/26	71 (39-87)	83.9	2.8 (0.6; 5.0)	2.8 (0.6; 5.0)
ENDOMODEL (LINK)	211	81/19	72 (46-89)	67.5	1.1 (0.0; 2.6)	3.1 (0.0; 7.1)

Key: obs. = observations; CI = confidence interval. ; OA = osteoarthritis
Note: Missing revision rates were marked with "- (-; -)". This can be due to two main reasons: the estimates at the given follow-up can be calculated but are highly biased by the low number of observations (too many patients have been lost at follow-up); the knee system was recently adopted in clinical practice (no patients have reached yet the 5 years follow-up).
[a] *NEXGEN = all the variants of the model NEXGEN (i.e., CR, LPS, CR FLEX, LPS FLEX, GENDER, LCCK).*

Table 7.9: Data from New Zealand Joint Replacement Register (NZJRR) showing revision rates at 3 and 5 years by variables of the receiving population. These systems are all cemented except the last 3 (SCORPIO, MAXIM, and INSALL/BURSTEIN) for which the methods of fixation is not reported.

Knee system (cemented)	Total obs.	Female/Male [%]	Mean age (range)	OA [%]	3 years (95% CI)	5 years (95% CI)
LCS (DEPUY)	6,664	53/47	69 (22-94)	91	1.6 (-; -)	2.6 (-; -)
P.F.C. SIGMA (DEPUY)	4,524	50/50	68 (21-94)	94	1.6 (-; -)	2.1 (-; -)
GENESIS II (SMITH & NEPHEW)	4,283	53/47	68 (15-93)	93	1.7 (-; -)	2.5 (-; -)
DURACON (STRYKER)	3,269	55/45	70 (30-97)	91	1.1 (-; -)	1.3 (-; -)
NEXGEN CR (ZIMMER)	3,205	52/48	68 (14-92)	93	1.2 (-; -)	1.9 (-; -)
NEXGEN LPS (ZIMMER)	1,903	56/44	69 (18-93)	93	2.0 (-; -)	3.6 (-; -)
TRIATHLON (STRYKER)	1,855	53/47	69 (39-98)	96	0.0 (-; -)	- (-; -)
NEXGEN LPS FLEX (ZIMMER)	1,756	52/48	68 (28-93)	94	1.9 (-; -)	5.3 (-; -)
AGC (BIOMET)	372	58/42	72 (43-90)	93	1.1 (-; -)	1.3 (-; -)
MBK (ZIMMER)	222	48/52	66 (35-88)	89	3.2 (-; -)	4.2 (-; -)
SCORPIO (STRYKER) nr	842	55/45	70 (27-98)	95	2.8 (-; -)	3.9 (-; -)
MAXIM (BIOMET) nr	819	54/46	69 (20-89)	93	0.6 (-; -)	1.0 (-; -)
INSALL/BURSTEIN (ZIMMER) nr	249	54/46	68 (36-91)	85	6.4 (-; -)	9.6 (-; -)

Key: obs. = observations; CI = confidence interval; OA = osteoarthritis; nr = method of fixation not reported.
Notes: Missing revision rates were marked with "- (-; -)". This means that estimates at follow-up can not be calculated yet (e.g. the number of observations was too low for survival analysis or the follow-up did not reach 3 years). The horizontal black line divides knee systems for which methods of fixation was not reported.

Table 7.10: Data from New Zealand Joint Replacement Register (NZJRR), showing revision rates at 3 and 5 years by variables of the receiving population. This table refers to uncemented fixation only.

Knee system (uncemented)	Total obs.	Female/Male [%]	Mean age (range)	OA [%]	3 years (95% CI)	5 years (95% CI)
LCS (DEPUY)	2,347	43/57	64 (18-90)	94	3.9 (-; -)	5.0 (-; -)
DURACON (STRYKER)	704	43/57	68 (21-91)	94	1.4 (-; -)	1.4 (-; -)
NEXGEN CR (SMITH & NEPHEW)	306	49/51	69 (35-89)	89	2.5 (-; -)	3.2 (-; -)

Key: obs. = observations; CI = confidence interval; OA = osteoarthritis.
Notes: Missing revision rates were marked with "- (-; -)". This means that estimates at follow-up can not be calculated yet (e.g. the number of observations was too low for survival analysis or the follow-up did not reach 3 years).

We decided to stratify revision rate data from registers by age groups and included patients aged 50 and over. This choice was motivated by the observation of epidemiological data recorded by the Italian SDO system. Patients in the age group 50 and above represented more than 90% of the total procedures performed within the ICD-9-CM code 81.54. Several authors have shown that performance of knee implants is related to the activity level of the receiving patients. This may explain the observed revision rates in young and active patients that appear higher compared to elderly people[38,39].

To incorporate revision rates in our economic evaluations, we obtained further data from responding registries (Australia and Emilia-Romagna) for patients aged 50 and over. Data obtained from AOAJRR are reported in Tables 7.11 to 7.13; data collected from RIPO are reported in Tables 7.14 to 7.16.

Table 7.11: Data from the Australian Orthopaedic Association National Joint Replacement Register (AOAJRR) showing revision rates at 5 years for patients aged 50 and over who received cemented systems.

Knee systems (cemented fixation)	Total obs. in patients aged 50 and over	5 years (95% CI)
GENESIS II (SMITH & NEPHEW)	9,726	3.4 (2.9; 3.9)
P.F.C. SIGMA (DEPUY)	8,775	2.7 (2.2; 3.3)
DURACON (STRYKER)	8,039	3.1 (2.7; 3.6)
NEXGEN CR (ZIMMER)	7,013	1.7 (1.3; 2.2)
NEXGEN LPS FLEX (ZIMMER)	6,449	3.3 (2.5; 4.2)
GENESIS II OXINIUM (SMITH & NEPHEW)	6,049	4.5 (3.5; 5.6)
SCORPIO (STRYKER)	5,045	3.5 (2.9; 4.3)
LCS (DEPUY)	4,040	4.9 (4.2; 5.7)
NEXGEN LPS (ZIMMER)	3,742	2.8 (2.2; 3.4)
PROFIX (SMITH & NEPHEW)	3,425	3.8 (3.1; 4.7)
AGC (BIOMET)	2,605	3.0 (2.3; 4.0)
KINEMAX PLUS (STRYKER)	1,659	2.8 (2.1; 3.8)
NATURAL KNEE (ZIMMER)	1,149	1.8 (1.1; 3.0)
OPTETRAK-PS (EXACTECH)	979	6.9 (4.9; 9.5)
RBK SYSTEM (G.M.T.)	605	3.1 (1.7; 5.7)
MAXIM (BIOMET)	535	4.5 (2.8; 7.2)
ADVANCE (WRIGHT)	521	6.6 (4.6; 9.4)
ZIMMER MBK (ZIMMER)	284	4.7 (2.8; 8.0)
BALANSYS (MATHYS)	227	3.3 (1.4; 7.8)
I/B II (ZIMMER)	199	6.8 (4.0; 11.4)
APOLLO (ZIMMER)	166	0.6 (0.1; 4.2)
ADVANTIM (WRIGHT)	118	0.8 (0.1; 5.9)
GENESIS (SMITH & NEPHEW)	112	6.7 (3.3; 13.6)
OXFORD TMK (BIOMET)	71	1.4 (0.2; 9.6)
SERIES 7000 (STRYKER)	67	1.5 (0.2; 10.3)
AMK (DEPUY)	55	13.0 (6.4; 25.3)

Key: obs. = number of observations; CI = confidence interval; G.M.T. = Global Manufacturing Technology.
Note: This table only reports those knee systems for which revision rates were available.

Table 7.12: Data from the Australian Orthopaedic Association National Joint Replacement Register (AOAJRR) showing revision rates at 5 years for patients aged 50 and over who received uncemented systems.

Knee systems (uncemented fixation)	Total obs. in patients aged 50 and over	5 years (95% CI)
NEXGEN CR (ZIMMER)	5,742	2.0 (1.6; 2.5)
SCORPIO (STRYKER)	3,277	4.0 (3.1; 5.0)
DURACON (STRYKER)	2,882	3.5 (2.7; 4.4)
ACTIVE KNEE (ASDM)	2,382	3.9 (3.0; 5.0)
LCS (DE PUY)	2,233	3.9 (3.2; 4.9)
RBK SYSTEM (G.M.T.)	1,898	2.5 (1.8; 3.6)
NATURAL KNEE (ZIMMER)	1,642	3.4 (2.5; 4.5)
PROFIX (SMITH & NEPHEW)	894	3.6 (2.3; 5.6)
ADVANTIM (WRIGHT)	565	1.6 (0.8; 3.4)
MAXIM (BIOMET)	561	2.8 (1.7; 4.5)
ROTAGLIDE+ (CORIN)	345	4.1 (2.3; 7.3)
ADVANCE (WRIGHT)	286	4.5 (2.5; 8.0)
INTERAX (STRYKER)	50	6.5 (2.1; 18.8)

Key: obs. = number of observations; CI = confidence interval; ASDM = Advanced Surgical Design & Manufacture; G.M.T. = Global Manufacturing Technology.
Note: This table only reports those knee systems for which revision rates were available.

Table 7.13: Data from the Australian Orthopaedic Association National Joint Replacement Register (AOAJRR) showing revision rates at 5 years for patients aged 50 and over who received hybrid systems.

Knee systems (hybrid fixation)	Total obs. in patients aged 50 and over	5 years (95% CI)
DURACON (STRYKER)	6,778	3.2 (2.8, 3.8)
SCORPIO (STRYKER)	6,358	3.5 (2.9, 4.1)
NEXGEN CR (ZIMMER)	5,284	2.2 (1.7, 2.9)
P.F.C. SIGMA (DEPUY)	4,767	3.7 (3.0, 4.4)
GENESIS II (SMITH & NEPHEW)	3,038	3.5 (2.8, 4.4)
LCS (DEPUY)	2,111	3.7 (2.9, 4.7)
MAXIM (BIOMET)	1,248	2.9 (1.9, 4.3)
AGC (BIOMET)	1,107	1.9 (1.1, 3.1)
NATURAL KNEE (ZIMMER)	1,069	2.4 (1.5, 3.7)
PROFIX (SMITH & NEPHEW)	676	3.9 (2.5, 6.1)
NEXGEN LPS (ZIMMER)	608	4.9 (2.6, 9.2)
OPTETRAK-CR (EXACTECH)	226	3.3 (1.5, 7.3)
ZIMMER MBK (ZIMMER)	170	1.9 (0.6, 5.8)
AMK (DEPUY)	142	4.3 (2.0, 9.3)
APOLLO (ZIMMER)	111	0.9 (0.1, 6.3)
TRAC (BIOMET)	87	7.1 (3.3, 15.2)

Key: obs. = number of observations; CI = confidence interval.
Note: This table only reports those knee systems for which revision rates were available.

Table 7.14: Data from Registro dell'Implantologia Protesica Ortopedica (RIPO, Register of the Orthopaedic Prosthetic Implants) of Emilia-Romagna showing revision rates at 5 years for patients aged 50 and over who received cemented systems.

Knee systems (cemented fixation)	Total obs. in patients aged 50 and over	5 years (95% CI)
PROFIX (SMITH & NEPHEW)	3,698	2.4 (1.7; 3.1)
NEXGEN LPS (ZIMMER)	2,480	2.0 (1.4; 2.6)
GENESIS II (SMITH & NEPHEW)	861	1.5 (0.3; 2.7)
SCORPIO (STRYKER)	618	1.7 (0.6; 2.8)
INTERAX (STRYKER)	592	4.2 (2.5; 6.0)
OPTETRAK (EXACTECH)	577	2.8 (0.8; 4.7)
ADVANCE (WRIGHT)	508	3.3 (0.8; 5.7)
AGC V2 (BIOMET)	471	1.8 (0.2; 3.4)
ROTAGLIDE+ (CORIN)	385	2.9 (1.1; 4.7)
913 (LINK)	353	1.3 (0.0; 2.6)
NEXGEN CR (ZIMMER)	326	0.4 (0.0; 1.2)
GKS PRIME (PERMEDICA)	242	1.8 (0.0; 3.8)
PERFORMANCE (BIOMET)	238	3.2 (1.0; 5.5)
LCS (DEPUY)	238	4.1 (1.5; 6.8)
HLS NOETOS (TORNIER)	232	1.0 (0.0; 2.3)
DURACON II (STRYKER)	205	2.6 (0.4; 4.8)
ENDOMODEL (LINK)	199	1.2 (0.0; 2.8)
T.A.C.K. (LINK)	67	6.1 (0.3; 11.8)

Key: obs. = number of observations; CI = confidence interval.
Notes:

i) This table only reports those prostheses for which there is more than 1 observation and meaningful revision rates.
ii) We decided not to report knee systems for which the estimates at the given follow-up were made unstable by the low number of observations (a high number of patients lost at follow-up) or by the recent adoption of the knee systems (no patients had yet reached the 5 year follow-up mark).

Table 7.15: Data from Registro dell'Implantologia Protesica Ortopedica (RIPO, Register of the Orthopaedic Prosthetic Implants) of Emilia-Romagna showing revision rates at 5 years for patients aged 50 and over who received uncemented systems.

Knee systems (uncemented fixation)	Total obs. in patients aged 50 and over	5 years (95% CI)
NEXGEN CR (ZIMMER)	389	2.6 (0.7; 4.5)
LCS (DEPUY)	339	0.6 (0.0; 1.6)
NEXGEN LPS (ZIMMER)	170	4.4 (0.0; 9.3)
P.F.C. SIGMA (DEPUY)	165	1.3 (0.0; 3.1)

Key: obs. = number of observations; CI = confidence interval.

Notes:

i) This table only reports those prostheses for which there is more than 1 observation and meaningful revision rates.

ii) We decided not to report knee systems for which the estimates at the given follow-up were made unstable by the low number of observations (a high number of patients lost at follow-up) or by the recent adoption of the knee systems (no patients had yet reached the 5 year follow-up mark).

Table 7.16: Data from Registro dell'Implantologia Protesica Ortopedica (RIPO, Register of the Orthopaedic Prosthetic Implants) of Emilia-Romagna showing revision rates at 5 years for patients aged 50 and over who received hybrid systems.

Knee systems (hybrid fixation)	Total obs. in patients aged 50 and over	5 years (95% CI)
T.A.C.K. (LINK)	528	6.0 (3.8; 8.2)
SCORPIO (STRYKER)	274	3.3 (0.0; 6.7)
NEXGEN LPS (ZIMMER)	108	9.5 (0.7; 18.4)
ROTAGLIDE+ (CORIN)	88	4.7 (0.2; 9.3)
LCS (DEPUY)	63	2.5 (0.0; 7.3)
INTERAX (STRYKER)	63	1.6 (0.0; 4.7)

Key: obs. = number of observations; CI = confidence interval.

Notes:

i) This table only reports those prostheses for which there is more than 1 observation and meaningful revision rates.

iii) We decided not to report knee systems for which the estimates at the given follow-up were made unstable by the low number of observations (a high number of patients lost at follow-up) or by the recent adoption of the knee systems (no patients had yet reached the 5 year follow-up mark).

7.4. Final considerations on register data

As described in Chapter 6, we decided to privilege the use of register effectiveness data to populate our economic analysis. Tables 7.17 to 7.19 represent the summary of our findings. We decided not to report all the implant models for which the registers shared data with us since some models were not identified by our context analysis (and are probably not used in Italy). We only reported on those knee systems that were identified by the context analysis (see Chapter 5) as being available in Italy. The revision rates presented in these tables were used as effectiveness estimates to implement our cost-effectiveness model presented in the following chapter.

We noted a high degree of variation in revision rates from the two registers we considered (AOAJRR from Australia and the RIPO from Emilia-Romagna). We explained these as the fact that the AOAJRR is a national register whilst RIPO is regional. National data could be more varied com-

pared to those from a single region in which surgical practice (and maybe outcomes) are more likely to be similar. The study of how contextual variables (e.g. number of procedures performed by the surgeon or by the hospital) affect the outcomes in orthopaedic prosthetic surgery is not part of the objectives of the present HTA report. However, this research question is being addressed by the national research project, "Strumenti e metodi per il governo dei processi di innovazione tecnologica, clinica ed organizzativa nel Servizio Sanitario Nazionale – Un sistema integrato di ricerca" coordinated by Agenas and currently underway.

Table 7.17: Revision rates of cemented knee systems by implant model at 5 years of follow-up. Estimates were calculated using Australia (AU) and Emilia-Romagna (ER) register data.

Knee system (cemented)	Level of evidence	Total obs. in patients aged 50 years and over	Source	5-years revision rate (95% CI)	
ADVANCE (WRIGHT)	2 registers	1,029	AU (521 obs.); ER (508 obs.)	AU = 6.6 (4.6; 9.4)	ER = 3.3 (0.8; 5.7)
AGC (BIOMET)	2 registers	3,076	AU (2,605 obs.); ER (471 obs.)	AU = 3.0 (2.3; 4.0)	ER = 1.8 (0.2; 3.4)
GENESIS II (SMITH & NEPHEW)	2 registers	10,587	AU (9,726 obs.); ER (861 obs.)	AU = 3.4 (2.9; 3.9)	ER = 1.5 (0.3; 2.7)
LCS (DEPUY)	2 registers	4,278	AU (4,040 obs.); ER (238 obs.)	AU = 4.9 (4.2; 5.7)	ER = 4.1 (1.5; 6.8)
NEXGEN CR (ZIMMER)	2 registers	7,339	AU (7,013 obs.); ER (326 obs.)	AU = 1.7 (1.3; 2.2)	ER = 0.4 (0.0; 1.2)
NEXGEN LPS (ZIMMER)	2 registers	6,222	AU (3,742 obs.); ER (2,480 obs.)	AU = 2.8 (2.2; 3.4)	ER = 2.0 (1.4; 2.6)
PROFIX (SMITH & NEPHEW)	2 registers	7,123	AU (3,425 obs.); ER (3,698 obs.)	AU = 3.8 (3.1; 4.7)	ER = 2.4 (1.7; 3.1)
SCORPIO (STRYKER)	2 registers	5,663	AU (5,045 obs.); ER (618 obs.)	AU = 3.5 (2.9; 4.3)	ER = 1.7 (0.6; 2.8)
BALANSYS (MATHYS)	1 register	227	AU (227 obs.)	3.3 (1.4; 7.8)	
DURACON (STRYKER)	1 register	8,039	AU (8,039 obs.)	3.1 (2.7; 3.6)	
DURACON II (STRYKER)	1 register	205	ER (205 obs.)	2.6 (0.4; 4.8)	
ENDOMODEL (LINK)	1 register	199	ER (199 obs.)	1.2 (0.0; 2.8)	
GENESIS II O. (SMITH & NEPHEW)	1 register	6,049	AU (6,049 obs.)	4.5 (3.5; 5.6)	
GKS PRIME (PERMEDICA)	1 register	242	ER (242 obs.)	1.8 (0.0; 3.8)	
HLS NOETOS (TORNIER)	1 register	232	ER (232 obs.)	1.0 (0.0; 2.3)	
NATURAL KNEE (ZIMMER)	1 register	1,149	AU (1,149 obs.)	1.8 (1.1; 3.0)	
NEXGEN LPS-FLEX (ZIMMER)	1 register	6,449	AU (6,449 obs.)	3.3 (2.5; 4.2)	
OPTETRAK (EXACTECH)	1 register	577	ER (577 obs.)	2.8 (0.8; 4.7)	
P.F.C. SIGMA (DEPUY)	1 register	8,775	AU (8,775 obs.)	2.7 (2.2; 3.3)	
RBK SYSTEM (G.M.T.)	1 register	605	AU (605 obs.)	3.1 (1.7; 5.7)	
ROTAGLIDE+ (CORIN)	1 register	385	ER (385 obs.)	2.9 (1.1; 4.7)	

Key: obs. = number of observations; CI = confidence interval; O. = Oxinium; G.M.T. = Global Manufacturing Technology.
The horizontal black line indicates lack of overlap (portion below) by prostheses with other registry data.

Table 7.18: Revision rates of uncemented knee systems by implant model at 5 years of follow-up. Estimates were calculated using Australia (AU) and Emilia-Romagna (ER) register data.

Knee system (uncemented)	Level of evidence	Total obs. in patients aged 50 years and over	Source	5-years revision rate (95% CI)	
LCS (DE PUY)	2 registers	2,572	AU (2,233 obs.); ER (339 obs.)	AU = 3.9 (3.2; 4.9)	ER = 0.6 (0.0; 1.6)
NEXGEN CR (ZIMMER)	2 registers	6,131	AU (5,742 obs.); ER (389 obs.)	AU = 2.0 (1.6; 2.5)	ER = 2.6 (0.7; 4.5)
ADVANCE (WRIGHT)	1 register	286	AU (286 obs.)	4.5 (2.5; 8.0)	
DURACON (STRYKER)	1 register	2,882	AU (2,882 obs.)	3.5 (2.7; 4.4)	
NATURAL KNEE (ZIMMER)	1 register	1,642	AU (1,642 obs.)	3.4 (2.5; 4.5)	
NEXGEN LPS (ZIMMER)	1 register	170	ER (170 obs.)	4.4 (0.0; 9.3)	
P.F.C. SIGMA (DEPUY)	1 register	165	ER (165 obs.)	1.3 (0.0; 3.1)	
PROFIX (SMITH & NEPHEW)	1 register	894	AU (894 obs.)	3.6 (2.3; 5.6)	
RBK SYSTEM (G.M.T.)	1 register	1,898	AU (1,898 obs.)	2.5 (1.8; 3.6)	
ROTAGLIDE+ (CORIN)	1 register	345	AU (345 obs.)	4.1 (2.3; 7.3)	
SCORPIO (STRYKER)	1 register	3,277	AU (3,277 obs.)	4.0 (3.1; 5.0)	

Key: obs. = number of observations; CI = confidence interval; G.M.T. = Global Manufacturing Technology.
The horizontal black line indicates lack of overlap (portion below) by prostheses with other registry data.

Table 7.19: Revision rates of hybrid knee systems per implant model at 5 years of follow-up. Estimates were calculated using Australia (AU) and Emilia-Romagna (ER) register data.

Knee system (hybrid)	Level of evidence	Total obs. in patients aged 50 years and over	Source	5-years revision rate (95% CI)	
LCS (DEPUY)	2 registers	2,174	AU (2,111 obs.); ER (63 obs.)	AU = 3.7 (2.9, 4.7)	ER = 2.5 (0.0; 7.3)
NEXGEN LPS (ZIMMER)	2 registers	716	AU (608 obs.); ER (108 obs.)	AU = 4.9 (2.6, 9.2)	ER = 9.5 (0.7; 18.4)
SCORPIO (STRYKER)	2 registers	6,632	AU (6,358 obs.); ER (274 obs.)	AU = 3.5 (2.9, 4.1)	ER = 3.3 (0.0; 6.7)
AGC (BIOMET)	1 register	1,107	AU (1,107 obs.)	1.9 (1.1, 3.1)	
DURACON (STRYKER)	1 register	6,778	AU (6,778 obs.)	3.2 (2.8, 3.8)	
GENESIS II (SMITH & NEPHEW)	1 register	3,038	AU (3,038 obs.)	3.5 (2.8, 4.4)	
NATURAL KNEE (ZIMMER)	1 register	1,069	AU (1,069 obs.)	2.4 (1.5, 3.7)	
NEXGEN CR (ZIMMER)	1 register	5,284	AU (5,284 obs.)	2.2 (1.7, 2.9)	
P.F.C. SIGMA (DEPUY)	1 register	4,767	AU (4,767 obs.)	3.7 (3.0, 4.4)	
PROFIX (SMITH & NEPHEW)	1 register	676	AU (676 obs.)	3.9 (2.5, 6.1)	
ROTAGLIDE+ (CORIN)	1 register	88	ER (88 obs.)	4.7 (0.2; 9.3)	

Key: obs. = number of observations; CI = confidence interval.
The horizontal black line indicates lack of overlap (portion below) by prostheses with other registry data.


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8. Economic model and cost-effectiveness analysis of knee prostheses

8.1 Introduction

Having estimated costs of prostheses and their effects on the basis of available data on prices and implant survival rates, in this chapter we will estimate the incremental cost-effectiveness of prosthesis which we are certain are bought and used in Italy. We will adopt the perspective of the INHS to construct our economic model. This is a narrower perspective than a societal perspective but it is consistent with that of our commissioners the Ministerial Committee on Medical Devices (CUD – Commissione Unica Dispositivi medici). Another reason for assuming the INHS perspective is its simplicity. In a country in which routine good quality data is not easy to retrieve, our model can furnish a useful and quick means of carrying out a "macro stratification" of prostheses (or any other implantable device) by selecting firstly those for which data are available, then those for which data are available from different sources, then those for which these data can be combined into cost-effectiveness ratios. Although imperfect, because of the attrition of data due to different reasons (see discussion at chapter 9), this simple model is better than no model or basing decisions on prostheses cost alone. A more accurate model would be based on a complete list of TKR prostheses available in Italy, 100% coverage of regional purchasing prices of all prostheses and effectiveness estimates (for example implant survival rates) based on prospective nominal cohorts of recipients. Nominal cohorts would have a numerator identifying each recipient by name and prosthesis model. This would allow active follow-up up of each recipient for a period of 5 to 10 years. Active follow up would entail longitudinal monitoring. This in turn would ensure that attrition (i.e. to loss to follow up such as deaths) would impact on the survivors and the cohort would get smaller with the passing of time. The cause for each loss would have to be investigated and its relationship with the implant and its insertion assessed. The magnitude and resource necessary for such a sophisticated methodological approach is quite beyond the resources available to any of the registers we identified and its utility, beyond theory would have to be demonstrated.

8.2 Methods

We stratified all prosthesis by classes (see chapter 5) and identified price and revision rate for each. The data are taken from those in Tables 5.5 and 7.17 respectively. We calculated the implant survival rate (as 100 - revision rate) to calculate the Incremental Cost Effectiveness Ratio (ICER) in 2009 Euros. Direct costs of each implant (i.e. those accruing to the INHS) are thought to be similar within prosthesis design classes. For this reason we did not incorporate them in our comparisons. For each prosthesis we calculated the ICER expressed as an incremental cost per revision avoided over a 5-year period. ICERs synthesises the relation between the cost of each prostheses and clinical effectiveness compared with each other.

We calculated ICERs only for classes for which cost and effect data were available for two or more prostheses as follows:

$$ICER = \frac{(Cbs - Cn)}{implant\ \ survival\ rate\,(bs) - implant\ survival\ rate\,(n)}$$

where:

Cbs = Cost of base line prosthesis
n = comparative prosthesis
Cn = Cost of comparative prosthesis
Implant survival rate = 100 – revision rate

8.3 Results

We identified the base line prosthesis (BS) as the prosthesis with the lowest revision rate (i.e. those for which there is the highest evidence of patient benefit). We did this using survival data from the 2 registers (Register of the Orthopaedic Prosthetic Implants - RIPO and Australian Orthopaedic Association National Joint Replacement Register - AOAJRR) by class of prosthesis.

The base line prosthesis was chosen on the basis of its 5 year clinical performance. As each base line prosthesis can be considered as the best performing within its class, all other prosthesis should be compared with these. However the highest effectiveness may not necessarily mean the highest cost-effectiveness as the latter is the ratio of mean weighted cost to performance. Although it is marginal (or incremental) cost-effectiveness which should be used for decision making purposes the choice of starting the evaluation using the highest effectiveness simplifies the calculation considerably. If a regional decision maker consults the RIPO, he or she will be able to identify the most effective prostheses and then gather information on purchase costs and volumes of activity in his or her region following our methodology. This simple procedure will allow ICERs to be calculated simply and relatively quickly. However the limits of such an approach are similar to ours. These can be summed up with the phrase "you can only use what data you have". Regional decision-makers may be able to identify purchase and volume data for their regions but until their own regional registers are running and populated by data for a reasonable follow up period they can only construct ICERs from the two sets of data (cost and effect) which may not necessarily be for the same prostheses. For some cost and effectiveness data will be available. For others only one or the other, and effectiveness data will necessarily be that of devices used in Emilia-Romagna (or Australia). These considerations should be a further stimulus for all stakeholders to coordinate the birth and development of prostheses registers and rolling regional surveys of devices on the market and their costs.

We calculated differences in cost and effectiveness ($\triangle$C and $\triangle$E) compared to the ICER of the baseline prosthesis. A positive $\triangle$C means that the baseline prostheses is more costly than its comparator, while a negative cost difference means the opposite. Instead $\triangle$E are all positive as the baseline prostheses is always the most effective. Finally we have included the knee prosthesis revision DRG (DRG 209 - Decree of the Ministry of Health - 12/09/2006) to compare ICERs using a value expressing the INHS desirability of avoiding revision sustainability. If the ICER is greater than the DRG reimbursement value the INHS is burdened with a further cost and a revision may be preferable.

However in the absence of meaningful quality of life data, such a value judgement is very difficult to make. We could not identify comparators for medial pivot, linked and tricondylar prostheses.

8.3.1 Results using RIPO data

According to RIPO data in the class of multiradius the prosthesis with the highest effectiveness is GENESIS II. We defined this as our base line. The following tables are referred only to cemented prostheses. For each model the table reports costs weighted by number purchased and the 5 year survival rate.

Table 8.1 shows that GENESIS II is dominant when compared with AGC and LCS as shown by their negative ICER which indicates that GENESIS II is more cost-effective than its two comparators. However NEXGEN LPS is more cost-effective than the baseline (with ICER of € 575,46, expressing the cost per avoided revision compared to baseline. In other words, using NEXGEN LPS instead of GENESIS II would save the INHS € 575. This is still less than the cost of prosthesis revision procedure (€ 8,777).

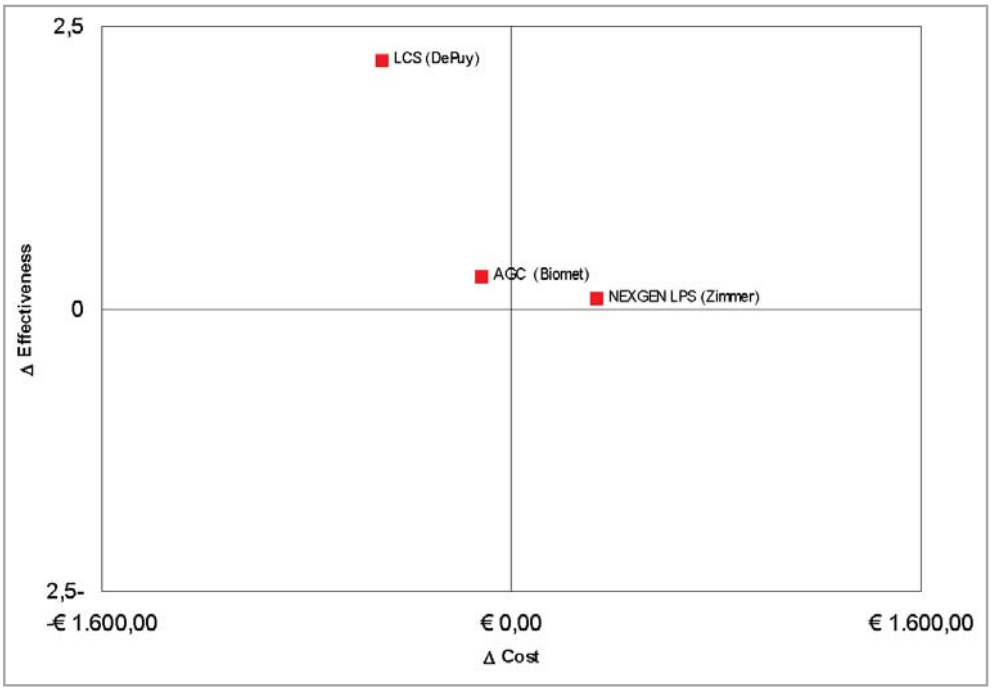
Table 8.1: ICER (RIPO data) for multiradius femoral class – Prosthesis base line: GENESIS II

MODEL NAME (Manufacturer)	MEAN WEIGHTED PRICE 2007 (€)	REVISION RATE at 5 years (%)	IMPLANT SURVIVAL RATE at 5 years (%)	△C*	△ E**	ICER
AGC (Biomet)	€ 3.057,80	1,8	98,2	- € 116,80	0,3	- € 477,11
LCS (DePuy)	€ 3.450,00	4,1	95,9	- € 509,00	2,6	- € 283,55
GENESIS II (Smith&Nephew)	**€ 2.941,00**	**1,5**	**98,5**	**Base line prosthesis**		
NEXGEN LPS (Zimmer)	€ 2.609,38	2	98	€ 331,62	0,5	€ 575,46

Source: Agenas elaboration
** △C = 2007 cost difference between base line and comparator prostheses*
***△E = effectiveness difference between base line and comparator prostheses*
NB: a minus sign means lower cost-effectiveness compared to base line

Figure 8.1 shows prostheses ICERs as dots scattered around the axis. The upper right hand quadrant includes models which are less effective than the base line model but have lower cost. The upper left had quadrant includes prostheses which have higher costs and lower effectiveness than baseline. NEXGEN LPS is the most cost-effective prosthesis as it is very near the zero value, meaning that the difference in effectiveness is very small. Only NEXGEN LPS has similar cost-effectiveness.

Figure 8.1: Cost-effectiveness representation



SCORPIO has the highest effectiveness of single-radius design prostheses according to RIPO revision rates. SCORPIO is the dominant technology as it has the lowest cost and the lowest revision rate (Table 8.2). The negative ICER indicates the lower cost-effectiveness of PROFIX compared to SCORPIO which is not surprising given the premium price of the PROFIX femoral Oxinium component.

Table 8.2: ICER (RIPO data) for single-radius class – Prosthesis base line: SCORPIO

MODEL NAME (Manufacturer)	MEAN WEIGHTED PRICE 2007	REVISION RATE at 5 years (%)	IMPLANT SURVIVAL RATE at 5 years (%)	ΔC	ΔE	ICER
PROFIX (Smith & Nephew)	€ 4.609,28	2,4	97,6	- € 2.100,55	0,7	- € 3.000,79
SCORPIO (Stryker)	€ 2.508,73	1,7	98,3	Base line		

Source: Agenas elaboration

8.3.2 Results using AOAJRR data

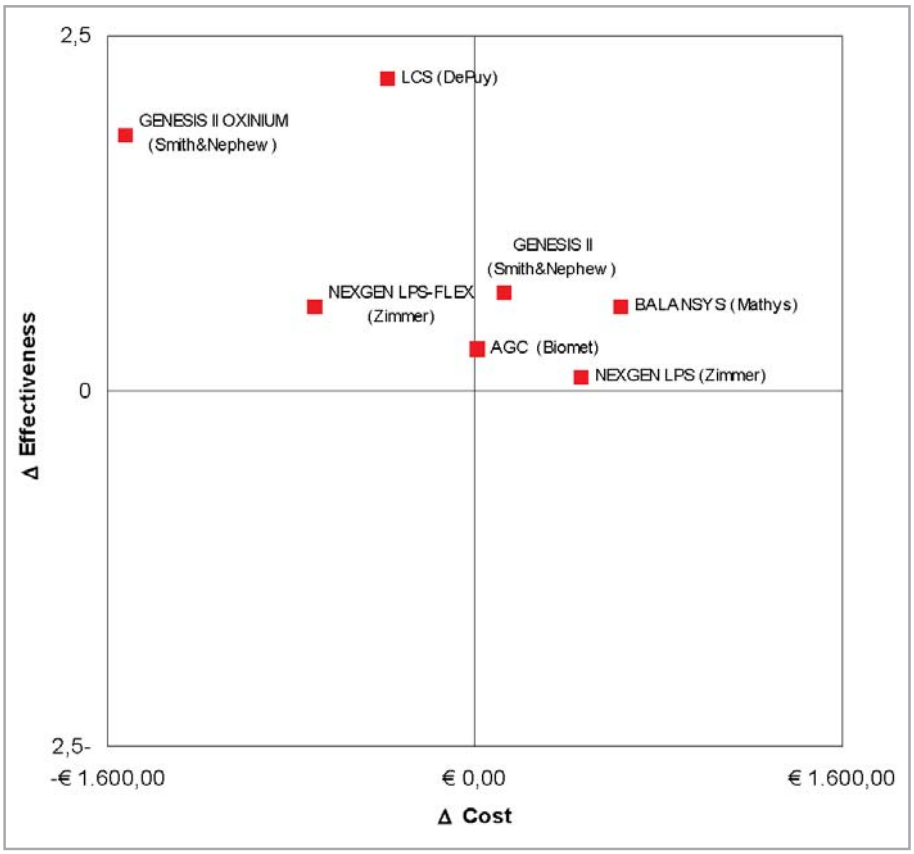
According to AOAJRR data, in the class of multiradius femoral design, the prosthesis with highest effectiveness is P.F.C. SIGMA. We defined this as our base line prosthesis. P.F.C. SIGMA is also the dominant prosthesis compared to LCS, GENESIS II OXINIUM and NEXGEN LPS-FLEX as shown by their negative ICERs. The other prosthesis types (AGC, BALANSYS, GENESIS II and NEX-GEN LPS) have a positive incremental cost as they are cheaper than base line (Table 8.3). The effectiveness differentials are all positive because by definition the baseline prosthesis is the most effective. Figure 8.2 shows graphically variations of costs and effects by model compared with the base line model. NEXGEN LPS has the highest cost-effectiveness as it has similar effectiveness (the difference against base line is 0,1%) but costs € 458,62 less than base line.

Table 8.3: ICER (AOAJRR data) for multiradius class – Prosthesis base line: P.F.C. SIGMA

MODEL NAME (Manufacturer)	MEAN WEIGHTED (PRICE 2007)	REVISION RATE at 5 years (%)	IMPLANT SURVIVAL RATE at 5 years (%)	△C*	△E**	ICER
AGC (Biomet)	€ 3.057,80	3	97	€ 10,20	0,3	€ 34,00
LCS (DePuy)	€ 3.450,00	4,9	95,1	- € 382,00	2,2	- € 173,64
P.F.C. SIGMA (De Puy)	**€ 3.068,00**	**2,7**	**97,3**	**Base line prosthesis**		
BALANSYS (Mathys)	€ 2.433,00	3,3	96,7	€ 635,00	0,6	€ 1.058,33
GENESIS II (Smith&Nephew)	€ 2.941,00	3,4	96,6	€ 127,00	0,7	€ 181,43
GENESIS II OXINIUM (Smith&Nephew)	€ 4.593,57	4,5	95,5	- € 1.525,57	1,8	- € 847,54
NEXGEN LPS-FLEX (Zimmer)	€ 3.771,00	3,3	96,7	- € 703,00	0,6	- € 1.171,67
NEXGEN LPS (Zimmer)	€ 2.609,38	2,8	97,2	€ 458,62	0,1	**€ 4.586,20**

Source: Agenas eleboration
* *△C = 2007 cost difference between base line and comparator prostheses*
** *△E = effectiveness difference between base line and comparator prostheses*
NB: a minus sign means lower cost-effectiveness compared to base line

Figure 8.2: Cost-effectiveness representation.



According to AOAJRR data, in the class single - radius femoral design, the prosthesis with highest effectiveness is SCORPIO. It is the dominant technology as it has the lowest cost and the lowest revision rate. Its comparator, PROFIX has a high price because of a femoral Oxinium component.

Table 8.4: ICER (AOAJRR data) for single radius femoral design – Prosthesis base line SCORPIO

MODEL NAME (Manufacturer)	MEAN WEIGHTED PRICE 2007	REVISION RATE	IMPLANT SURVIVAL RATE	Δ_C	Δ_E	ICER
PROFIX (Smith & Nephew)	€ 4.609,28	3,8	96,2	- € 2.100,55	0,3	- € 7.001,83
SCORPIO (Stryker)	€ 2.508,73	3,5	96,5	Base line		

Source: Agenas elaboration

8.4 Conclusions

Regardless of whether we included effectiveness data from RIPO or AOAJRR registers, NEX-GEN LPS (ZIMMER) is the most cost-effective among the prostheses with a multiradius femoral design while SCORPIO (STRYKER) is the most cost-effective among the prostheses with a single-radius design. ICERs were calculated comparing only prostheses in the same femoral design class. Using a different approach, ICERs could be calculated comparing prostheses with different biomechanical designs. ICERs of other prostheses are sensitive to the source of effectiveness estimates. The main limitations of our analysis and conclusions are mentioned in the Discussion (chapter 9).

9. Discussion

The present report was designed to assess whether the prostheses for TKR currently used in the Italian clinical practice are supported by evidence, and if implant performance can be correlated to implant price. We addressed these issues first by performing a context-specific analysis (to identify which knee systems are currently in use and their prices), a systematic review of the evidence from formal studies and an analysis of implant performance from the arthroplasty registers (to identify performance by knee system). Finally with the cost and the effectiveness data so far assembled, we carried out an economic evaluation to help decision making by the Italian MLHSP.

The context-specific analysis was necessary since the central inventory of medical devices was not yet operative at the start of the study (and is not completed yet at the time of writing). The survey allowed us to identify a list of knee systems that are probably representative of all the devices used in Italy, together with their mean purchasing prices. These prices can be assumed as "real prices", i.e. the true amount that purchasers have to pay in the transaction. "Real price" is sometimes different from the price reported in the manufacturer's list price as, to our knowledge, bulk purchase discounts are common.

Manufactures of knee prostheses were involved in our HTA project as stakeholders. We contacted several companies with a formal letter sent to the main association of manufacturers of medical technology in Italy (ASSOBIOMEDICA) but elicited scarce interest from manufacturers. Only 6 companies collaborated with us: BIOMET, DEPUY, LIMA, LINK, MEDACTA, and STRYKER out of the 25 or more which to our knowledge are active in Italy. No reply or reasons for non-response were received by the others.

We attempted to identify and synthesise evidence of performance (expressed as survival rate or revision rate for each knee system) from published literature. Unfortunately, literature in this field seems to be too generic for our particular research questions. Very few studies met our inclusion criteria and those that did were poorly reported. For this reason we decided to give more weight to performance estimates contained in the periodic reports of the arthroplasty registers. We were forced to refer to national registers of foreign countries, as Italy does not yet have a national knee prostheses register. At present a National hip arthroplasty register project is running and will start collecting data in the next months. In the near future, there is the intention to extend the same protocol to the knee arthroplasty registration. However, we used regional Italian data thanks to the collaboration and data-sharing spirit of the RIPO (regional register of Emilia-Romagna).

We noted high variation among the periodic reports published and decided to conduct an enquiry among the "key-persons" (e.g. the register's coordinator) of the arthroplasty registers to obtain collaboration in our project by data-sharing. Unfortunately, few collaborated. Some key persons reported that the data we asked for were not available for "third party" analysis, sometimes the data were not available at all as they were not collected on a regular basis. However we greatly benefited from the collaboration with the AOAJRR (the Australian register) and the RIPO. Their key persons sent all data we requested rapidly, sometimes performing ad hoc queries and handling.

The gross heterogeneity of reporting formats and attitudes coupled with the scarce evidence from literature meant that we were faced with a sizeable loss of data both on costs and effects, as we could not identify prostheses and assign costs and outcomes.

An additional problem is caused by the regulatory environment. In the current EU system prostheses can enter the market in the absence of clinical trial data or even of comparative data. The revised regulation at page 22 states that: "*As a general rule, confirmation of conformity with the requirements concerning the characteristics and performances referred to in Sections 1 and 2 of Annex 1 under the normal conditions of use of the device and the evaluation of the side-effects and of the acceptability of the benefit/risk ratio referred to in Section 5 of Annex 1, must be based on clinical data". Clinical data is defined as "the safety and/or performance information that is generated from the use of a device. Clinical data are sourced from:*

a) clinical investigation(s) of the device concerned, or

b) clinical investigation(s) or other studies reported in the scientific literature, of a similar device for which equivalence to the device in question can be demonstrated, or

c) published and/or unpublished reports on other clinical experience of either the device in question or a similar device for which equivalence to the device in question can be demonstrated." [40]*;*

With such vague guidance reliance on registers is the only possible solution. However no matter how well-kept and collaborative the register may be, meaningful performance of knee prostheses can only be judged after a number of years (ideally 10). By this time a new prosthesis often considered "better" than the existing ones has entered the market and has begun to supersede existing prostheses for which there is now better evidence. At this point the process has to start all over again, limiting the decision-making usefulness of any register for new devices recently introduced into a market.

Despite the limitations and constraints of our study we were able to show that purchase price and effectiveness per se are not sufficient to inform decision makers. What is required is the linking of the two into incremental cost-effectiveness ratios within prostheses design classes. It is essential however that performance is calculated on recipient categories which are broadly similar in terms of age, gender, indications and whenever possible, BMI.

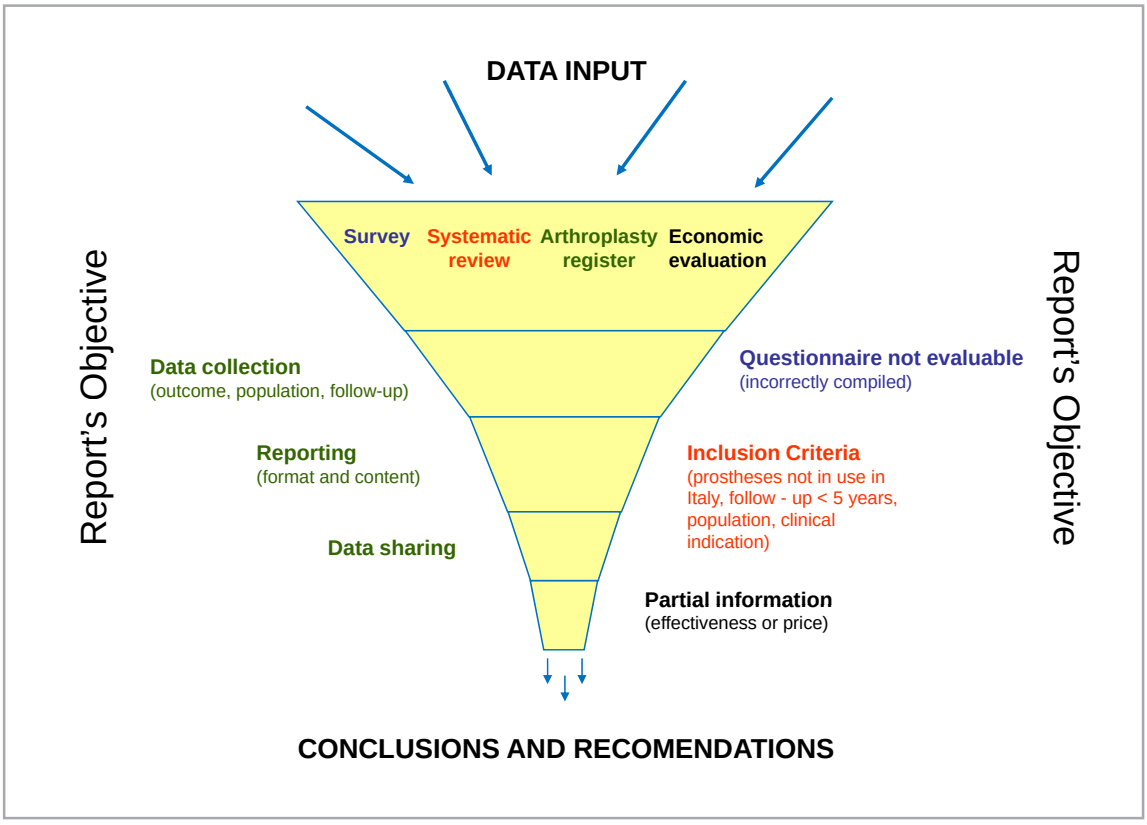
According to our calculations the most cost-effective multiradius prosthesis in those aged 50 or more is NEXGEN LPS (Zimmer), whereas Scorpio (Styker) is the most cost-effective singleradius prostheses. Our conclusions are insensitive to the inclusion of effectiveness data from RIPO or AOAJRR. Little can be said for the remaining class which had only one prostheses per stratum, but our ICERs provide at least some benchmarking for similar prostheses accruing sufficient survival data in the future.

There are several limits to our analysis. The random sampling structure and relatively low returns from our questionnaire meant that not all high throughput orthopaedic centres offering TKR were sampled or responded. Whereas the former is a limitation of sampling which is obviated by the sample's representativness, this could have been undermined by the response rate despite its good geographic spread. We personally solicited responses from all sampled centres but we cannot be absolutely sure of the samples representativeness.

The data loss due to a narrow study question, inclusion criteria, 5 year survival cut-off, and focused outcomes is another potential limit of our study (see figure 9.1 that depicts the various levels and causes of data loss through the study). For example the 50 year limit entailed the exclusion of some large studies which reported ages in aggregate or as ranges (i.e. 18-75). Some of these studies probably reported data which were relevant to our study, but had to be excluded to avoid confounding and preserving our focus on OA.

In addition, our analyses are based on costs and effectiveness estimates which may not be generalisable across nations or even regions of the same system. This is shown by the difference in some effectiveness profiles for the same model of prostheses between the two registers. The availability of more individual data from registers would have allowed more sophisticated comparisons to be made, adjusted for example by risk factors such as level of physical activity, age and co-morbidities. Finally, one of the manufacturers also told us that our weighted costs estimates grossly overestimated the costs of their products, probably unfavourably impacting on their ICERs. While this may be so, we had to rely on what respondents told us. Their cost data in turn reflected local purchase prices, i.e. reality.

Figure 9.1: Flow of data loss through the study.

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10. Recommendations

We recommend that:

- Purchasers and decision makers privilege first the best performing prostheses within the class and second those for which there is more evidence of good performance at the 5 year point.
- New knee prostheses be tested in adequately designed evidence-generating programmes in the EU.
- Following the consolidated experience of other countries and of the already existing Italian regional registries, a national knee arthroplasty registry should be organised in a short period. The structure adopted for the Italian national arthroplasty registry consisting in a federation of regional registries coordinated by the ISS, using as a support for the data collection the discharge records integrated with additional information regarding the patient and the device, should be taken into account. As already performed in the Swedish registry, the assessment of sampled patients health related quality of life should be included in the protocol.


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12. Competing interests declaration

The authors declare that they will not receive either benefits or harms from the publication of this report. None of the authors have or have held shares, consultancies or personal relationships with any of the producers of the devices assessed in this document.

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Appendix 1

Technological characteristics of knee prostheses

Total joint implants

Total joint prostheses are permanent implants mimicking the natural biomechanics of the natural joints. Since extensive bone and cartilage are removed during implantation, joint replacement is an irreversible procedure. Presently, joint implants are performed in the hip, knee, shoulder, ankle, elbow, wrist and fingers.

For a "perfect" total joint implant, a number of issues must be considered (Bronzino, 2000):

- overloading and load-shielding of implant-bone interface may result in bone remodelling with a consequent loosening of the implant;
- the articulating surfaces should work with minimum friction and should produce the least amount of wear debris;
- the implant should be quickly and tightly fixed to the bone (ideally, immediately after implantation);
- removal of the implant (revision procedure) should not require the destruction of a large amount of surrounding tissues.

Prostheses for primary TKR

Prostheses for primary TKR are also called tri-compartmental knee prostheses or total knee prostheses since all the compartments of the joint (medial, lateral and patellofemoral) are replaced. For the replacement of only one of the femoral condyles, unicompartmental (or unicondylar) prostheses are used (see orthopedics website, totaljoints website). As previously stated, this report is focused only on prostheses for primary TKR. Unicompartmental or patello-femoral designs are not assessed or mentioned in this report.

From a biomechanical point of view, the knee joint is a complex joint since the articulating surfaces roll and glide as the knee bends and straightens. The large muscles of the leg provide strength while ligaments provide stability to the articulation. Three bones are involved in the knee: the femur, the tibia and the patella. The articular cartilage covers the bearing surfaces and when it becomes damaged pain occurs.

The first designs of artificial joints adopted the concept of the hinge mechanism between the components. More recent designs, attempt to emulate the natural movement and take advantage of the ligaments for support (Victor, 2006; Jacobs, 2005).

Many types of artificial knee joints are commercially available, but all have in common:

- a femoral component: a large block used to cover the distal part of the femur. The metallic part encapsulates the bone and has an internal groove in which the patella slides up and down permitting the knee to bend and straighten;

- a tibial component: a metallic plate (also called tibial tray) that is applied to the proximal part of the tibia;
- an insert: a plastic layer that is inserted onto the tibial plate and articulates with the femoral component. It presents a toroidal surface and may have a raised central ridge.

Sometimes a patellar component is used to replace the natural patella. It consists of a block of plastic (usually polyethylene) having the form of a cupola that imitates the shape of the patella.

The choice of the prosthesis is based on the patient's characteristics (e.g. age, weight, activity level), the implant's characteristics (e.g. design, materials), and the surgeon's experience and familiarity with the device (see totaljoints website; Pritchett, 2004; Kuster, 2002).

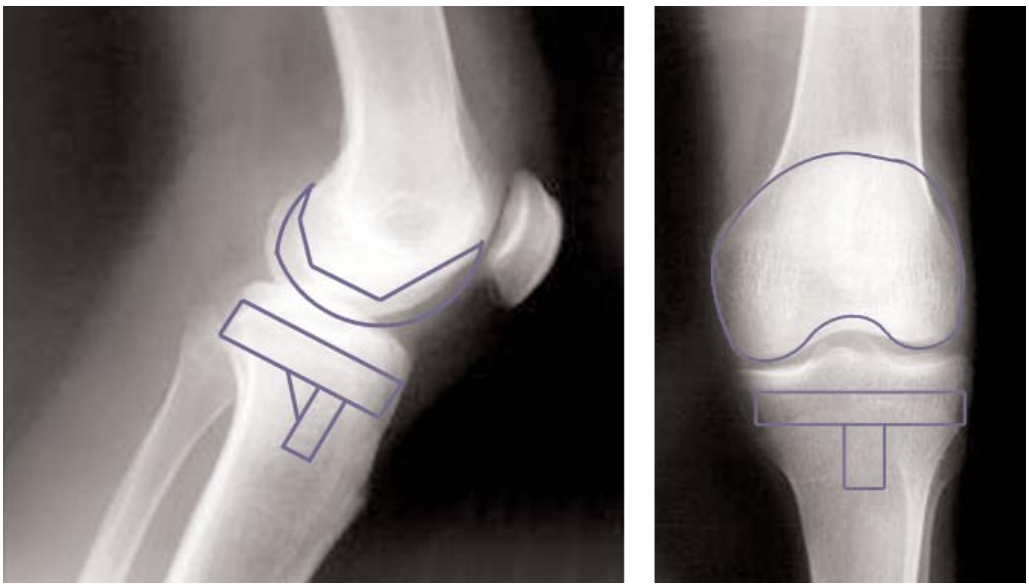
Prostheses for total knee replacement can also be classified according to other factors:

- the method of fixation of the components (cemented, uncemented or hybrid);
- the retention or the sacrifice of the posterior cruciate ligament;
- the type of plastic insert (that can be made by different types of polyethylene, fixed or mobile, and posterior stabilized or not).

Metal alloys are commonly used for femoral and tibial component, the insert is usually made of plastic and the patella may be all-plastic or metal-backed.

The selection of the best implant is quite complex: the variability of knee conditions is great and the number of choices in prosthesis types are significant.

Figure A1.1: Schematisation of a total knee implant. The plastic insert is not visible in radiographic images. Images were from www.sxc.hu



Materials used in TKR

Metal alloys

Components for cemented fixation are usually made of CoCrMo alloy (the composition varies between manufacturers and different registered names exist).

Titanium-based alloys (TiAlV) are used for cementless tibial components or for the surface coating of cobalt-based cementless components. Coating may be performed with several techniques that allow the creation of different kinds of micro and macro textures that promote osteointegration. Oxidized zirconium (OXINIUM) femoral components are also available.

Polymeric materials

Bone cement is consisting mainly of polymethylmetacrylate (PMM) and also contains crystals that make the resulting product radio-opaque (barium sulfate or zirconium oxide). Sometimes the bone cement is antibiotic-loaded. In TKR bone cement is used for fixation of femoral and tibial component. However, it acts as a filler not as a glue.

UHMWPE (Ultra-High Molecular Weight Polyethylene) is commonly used for the tibial insert and the patellar component.

Method of fixation

TKR performed by cemented fixation is considered the gold standard (Silverton, 2006).

Cemented fixation of the knee implant continues to be the most common method worldwide. Hybrid fixation is almost always performed by cementing the tibial component and only occasionally the femoral component (see Australian, Canadian, Danish and Swedish Registers).

However, if performed in young and very active patients (between the ages of 40 and 59 years), cemented knee systems may be subjected to failure mechanisms (aseptic loosening with fragmentation and debonding of the cement). For this reason, the biologically adaptive fixation phenomena characterising the modern cementless implant designs represent a very promising trend. Moreover, cementless fixation could be beneficial to the patient, surgeon, and hospital to minimise the waiting time in the operating room resulting from cement curing (Meneghini and Hanssen, 2008).

With the emergence of improved biomaterials, particularly porous tantalum and porous titanium, long-term success of some cementless designs is expected (Levine, 2007).

However, technique, adequate balancing of the soft tissues, and proper overall alignment must be accurately managed since each of them can lead to implant failure in any TKR system (cemented, cementless or hybrid).

Retention or sacrifice of the posterior cruciate ligament

In the healthy knee the posterior cruciate ligament (PCL) is responsible for the posterior translation of the femur onto the tibia during flexion. The PCL is the strongest ligament and prevents opening of the joint in flexion. After TKR, it is desirable that the natural knee movements and stability should be reproduced during the whole range of motion.

The factors influencing the choice of either removal or retention are the degenerative status of the PCL, the type of implant used, or just the personal preference of the surgeon.

Total knee systems that allow retention of PCL, generally present a thin insert with congruent surface. If the PCL is removed (for the reasons mentioned above), a thicker polyethylene insert has to be used. The insert may present a central post (like a pillar) that articulates with the cam present in the femoral component (the so-called "cam and post" mechanism). This design is often defined posterior stabilised (Victor, 2006).

The effect of retention or removal of the PCL have been assessed by a systematic review (Jacobs, 2005a). Due to the limited number of studies, often characterised by low quality, no recommendations have been made in relation to the difference between retention or removal of the PCL, or between retention and removal accompanied by a posterior-stabilised design (Jacobs, 2005b).

Fixed or mobile bearing designs

Fixed-bearing designs present an insert firmly fixed onto the tibial plate. However, as the knee flexes and extends, rotational and micro or macro motions also occur based on the quality of the locking mechanism and these may cause polyethylene wear. To address this problem, mobile-bearing designs have been developed.

Mobile-bearing knee systems are distinguished from conventional, fixed-plate systems in that they allow dual-surface articulation between the insert and the femoral and tibial components (Greenwald and Heim, 2005).

Several papers have compared fixed and mobile bearing knee replacements (McEwen, 2005; Sharma, 2007), but with some important limitations due to different femoral articulation design, different polyethylene material, manufacturing process and sterilisation.

A recent in vitro comparative study showed that no significant differences exist between a fixed and a mobile bearing knee design with identical superior articulation between femur and gliding surfaces. The outcomes assessed were: wear rate, resulting knee kinematics, wear pattern characteristics and particle size distribution (Grupp, 2009).

Biomechanics of physiologic and replaced knee

Knee motion is based on the concept of the "coupled motion". Movements occur along different axis: rotation along the horizontal axis (flexion), translation along the sagittal axis (roll-back of the femur), rotation over the coronal axis (femoral external rotation) (Daniel, 1990).

In the physiologic knee the motion is primarily guided by the cruciate ligaments (anterior cruciate ligament, ACL, and posterior cruciate ligament, PCL) and by the surface geometry of the tibial plateau that appears concave in the medial side and convex in the lateral side.

When TKR is performed, both ligaments and tibial surfaces undergo relevant modifications. Both cruciate ligaments are sacrificed except in the case of "cruciate retaining" (CR) prosthetic designs, that preserve the PCL only. The tibial plateau is resected and substituted with a tibial plate that allows articulation with the femur by an insert acting as articular surface. Surface geometries of the insert may be various but, with current technology, the replaced knee cannot move exactly as the normal knee (Victor, 2006).

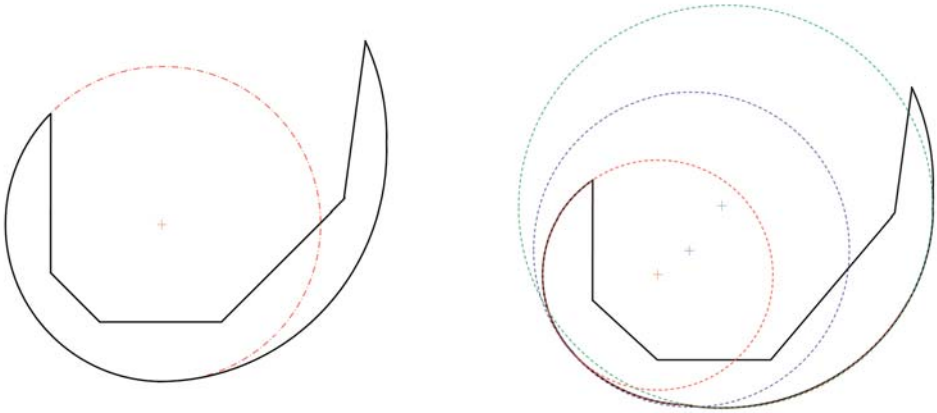
One of the aspects that knee designers have to consider is the biomechanics of the replaced knee. In particular, the non-conformity of the bearing surfaces: the radius of the femoral component does not match the radius of the tibial component throughout the flexion range (Kuster M, 2002). This is a peculiarity of the knee joint. In the past decades some different concepts have been applied with the aim to allow suitable biomechanical behaviour. Thus, taking account biomechanics, some major classes of prostheses may be identified.

- Multiradius femoral design;
- Single-radius femoral design;
- Medial pivot design;
- Tricondilar femural design;
- Linked, constrained or hinge systems.

Each of these designs present some particular characteristics that justify its use. Ideally, a multiradius femoral design may provide a wide range of motion while a single-radius design may reduce the surface stress from extension to full flexion throughout the complete flexion range (Kuster, 2002). However the dominance of one design compared to the other is still under debate (a recent randomised study showed no differences when the posterior cruciate ligament is retained) (Hall, 2008).

These designs (multiradius and single-radius) are the most common. Medial pivot design is more recent and presents an asymmetrical tibial insert, more congruent in the medial than in the lateral compartment, thus translation is limited around the congruent compartment and unrestricted in the other (Pritchett, 2004). Tricondylar design has been developed to reduce the stress on the tibial insert by a third condyle, placed between the two condyles, onto which the load is shared (Pinaroli, 2009). Linked, constrained or hinge systems present an important mechanical connection (a hinge) between the femoral and the tibial component. Such designs are used when medio-lateral stability is required and are not frequently used in primary TKR since they are indicated for patients with neuromuscular deficits (e.g. polio or flail knee).

Figure A1.2: Examples of femoral components with single-radius design (left) and multi-radius design (right).



State-of-the-art in Italy

To date, it seems virtually impossible to know how many total knee systems are available on the Italian market.

The prostheses identified by searches in the regional arthroplasty registers, on manufacturers' websites, or by the national survey is probably not exhaustive and may not represent the real number of devices used in Italy, that is probably higher.

However, through the Legge Finanziaria L. 266/2002, a central database containing all the medical devices available on the Italian market is under development. Such database, called RDM, Repertorio generale dei diapositivi medici (general archive of medical devices), will allow the collection of technical characteristics and price for each device purchasable by public hospitals.

In the future, only those medical devices for which the respective manufacturers have completed the RDM uploading procedures, will be able to be marketed in the Italian National Health System (INHS) (see MLSPS website).

The future

Total knee arthroplasty is currently a durable and cost-effective procedure for treatment of osteoarthritis of the knee joint (Räsänen, 2007). Recently it has been demonstrated that if performed in specialised hospitals, rather than general hospitals, the procedure has better results and fewer complications (Cram, 2007). The hospital and surgeon volume probably have an impact on this conclusion.

In the last decade, a number of new technologies have been introduced into the clinical practice of arthroplasty, some are very publicised and may represent important changes. For example,

new sequentially cross-linked polyethylene, minimally invasive TKR, computer-assisted or navigated TKR, and gender-specific designs.

However, as in all the therapeutic interventions, surgeons should use the practice of evidence-based medicine to adopt those surgical techniques that have been proven safe and efficacious by long-term prospective outcome studies (Richmond, 2009). Unfortunately, the marketing strategies also play their role and may guide the choices of surgeons and hospitals.

Minimally invasive procedures, are in general, considered very technically demanding. Computer navigation, that use precise identification systems of bony anatomic landmarks, may be used in combination with small incisions to allow the surgeon to obtain a better alignment of the prosthesis. Conversely, computer navigation requires a learning curve and is more expensive and time-consuming that the traditional surgery.

Recently new prostheses designs are introduced and marketed as "gender specific". The rationale of these devices is based on the anatomic variations between men and women. To date, there is no evidence to support an advantage of these gender-specific devices for women. When the literature for traditional TKR is reviewed for outcomes based on sex, the risk of failure is not higher in women than in men (Rankin, 2008).

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Appendix 2

Survey of Medical devices at 31st December 2007

"Knee prostheses"

REGIONAL CODE

CODE OF THE FACILITY

NAME OF THE FACILITY

INFORMATION OF THE MANAGER RESPONSABILE FOR THE UNIT

Name of the manager responsible for the compilation of this survey:

Identification of the Facility/Office:

Telephone:

e-mail:

IDENTIFICATION OF THE CONTACT PERSON (*)

Name of the person to be contacted for further information:

Identification of the Facility/Office:

Telephone:

e-mail:

**to be compiled if not the same person.*

PROCEDURE

ICD-9-CM 81.54 "Total knee replacement"

81.55 "Revision of the knee"

1. VOLUME OF ACTIVITY

N° of procedures 2007

- "Total knee replacement" (81.54):

- "Revision of the knee" (81.55):

2. BUYING METHOD

How are the knee prostheses purchased?

|___| Directly by the LHA/Hospital trust/other (specify)

|___| At a centralised level, options:

- |___| Regional
- |___| Larger area
- |___| Other

Knee prostheses- Primary intervention - YEAR 2006				
Model/Type	Manufacturer	Product code	Quantity	Unit price

Knee prostheses- Revision - YEAR 2006				
Model/Type	Manufacturer	Product code	Quantity	Unit price

Knee prostheses- Primary intervention - YEAR 2007				
Model/Type	Manufacturer	Product code	Quantity	Unit price

Knee prostheses- Revision - YEAR 2007				
Model/Type	Manufacturer	Product code	Quantity	Unit price

Appendix 3

Sampling methodology

The sample consists of a proportional stratified sample with random extraction of the units.

The sample was:

- stratified as the population is subdivided into subpopulations called strata;
- proportional as the allocation of sample units at different strata retain the same proportion with which they are present in the population;
- random as the sample units are drawn randomly from a list of units.

The sample was calculate as:

$$n = \left[\frac{\varepsilon^2 (N-1)}{NPQ} + \frac{1}{N} \right]^{-1}$$

where

n = sample size;

ε = standard error (set at 0,025);

N = Population (centres that had undertaken at least one primary total knee replacement or revision);

P = probability of primary total knee replacement is done;

Q = probability of revision total knee replacement is done;

P and Q (calculate using Hospital discharge records - SDO) were reported in Table A2.1.

After this stage sampling was made taking into account the proportional distribution of the population compared with strata (by Italian region) and substrate (by volume of activity) as follows:

- population strata of 21 Italian Regions and Autonomous Provinces (P.A.);
- determining the sample by strata substrata (three substrate for each strata);
- random extraction within substrata.

Sampling units was extracted using the following rate to each strata:

$$f = \frac{n}{N}$$

preserving, for each stratum, the proportions of structures for volumes of activity.

Finally, we increased the sample by 30% taking into account possible exclusion of incorrectly filled in questionnaires, non responses, and other cases. Table A2.2 shows sampling and population considered.

Table A2.1: Number of procedures per Italian region and type of procedures (2006).

Region	Absolute value			Value	
	Primary TKR	Revision TKR	Total	pi (primary TKR)	qi (revision TKA)
PIEMONTE	3927	186	4113	0,9548	0,045222
VALLE D'AOSTA	33	4	37	0,8919	0,108108
LOMBARDIA	8915	681	9596	0,9290	0,070967
BOLZANO	518	18	536	0,9664	0,033582
TRENTO	249	1	250	0,9960	0,004
VENETO	4957	238	5195	0,9542	0,045813
FRIULI V. GIULIA	1277	58	1335	0,9566	0,043446
LIGURIA	1343	90	1433	0,9372	0,062805
EMILIA ROMAGNA	5247	384	5631	0,9318	0,068194
TOSCANA	4150	279	4429	0,9370	0,062994
UMBRIA	1220	61	1281	0,9524	0,047619
MARCHE	1470	46	1516	0,9697	0,030343
LAZIO	3676	218	3894	0,9440	0,055984
ABRUZZO	1598	36	1634	0,9780	0,022032
MOLISE	167	1	168	0,9940	0,005952
CAMPANIA	2550	83	2633	0,9685	0,031523
PUGLIA	2704	118	2822	0,9582	0,041814
BASILICATA	334	8	342	0,9766	0,023392
CALABRIA	1028	51	1079	0,9527	0,047266
SICILIA	3271	166	3437	0,9517	0,048298
SARDEGNA	850	28	878	0,9681	0,031891
National	**49484**	**2755**	**52239**	**0,9473**	**0,05**

Table A2.2: Sample and total centres.

Region	Population				Sample (+ 30%)			
	N. centres	N. centres and volume			N. centres and volume			Total
		<50	50-350	> 350	< 50	50-350	> 350	
PIEMONTE	44	18	25	1	4	5	1	10
VALLE D'AOSTA	1	1	0	0	1			1
LOMBARDIA	113	61	50	2	10	8	1	19
BOLZANO	9	5	4	0	2	2		4
TRENTO	6	4	2	0	2	1		3
VENETO	36	8	25	3	2	5	1	8
FRIULI V. GIULIA	17	7	10	0	2	2		4
LIGURIA	15	6	9	0	2	2		4
EMILIA ROMAGNA	50	19	28	3	4	5	1	10
TOSCANA	44	12	31	1	3	5	1	9
UMBRIA	14	1	13	0	1	3		4
MARCHE	17	5	12	0	2	3		5
LAZIO	90	65	24	1	10	4	1	15
ABRUZZO	25	17	7	1	3	2	1	6
MOLISE	6	5	1	0	2	1		3
CAMPANIA	65	51	14	0	8	3		11
PUGLIA	39	21	17	1	4	3	1	8
BASILICATA	6	4	2	0	2	1		3
CALABRIA	22	16	5	1	3	2	1	6
SICILIA	80	60	19	1	9	4	1	14
SARDEGNA	22	14	8	0	3	2		5
Total	721	400	306	15	79	63	10	152
Total %	**100,00**	**55,48**	**42,44**	**2,08**	**51,97**	**41,45**	**6,58**	**100,00**

Key: N. = number.


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Appendix 4

List of responding centres

The Authors and Agenas would like to thank all the centres (clinical research institutes, private accredited providers, and public health services) who contributed to this HTA reports by participating to the survey. Centres are listed by region (north-south) and by code.

Piemonte:

010005	Ospedali Riuniti A.S.L. 14
010008	Ospedale Riuniti A.S.L. 19
010009	Ospedale Integrato A.S.L. 11
010011	Torino Nord Emergenza San G. Bosco
010902	Azienda Ospedaliera CTO M. Adelaide

Lombardia:

030045	Ospedale Civile Morbegno
030068	Ospedale di Circolo - Desio
030070	Ospedale Vittorio Emanuele III - Carate
030075	Presidio Ospedaliero "C. Cantu" - Abbiategrasso
030146	Istituto Suore Cappuccine di M. Rubatto - Casa di Cura S. Francesco Bergamo
030156	Ospedale di Desenzano del Garda (Bs)
030193	Ospedale Civile di Vigevano
030199	Casa di Cura Santa Maria delle Grazie s.r.l.
030227	Presidio Ospedaliero Asola
030355	Ospedale di Suzzara
030912	Azienda Ospedaliera ICP Milano

Autonomous Province of Bolzano:

041005	Azienda Sanitaria della P.A. di Bolzano - Comprensorio sanitario di Brunico
041011	Ospedale Generale di Zona Silandro

Veneto:

050017	Ospedale Sacro Cuore Don Calabria
050131	C.D.C. S.M. Maddalena
050202	Ospedale di Feltre
050209	Ospedale di Treviso
050215	Ospedali Azienda ULSS Alta Padovana
050218	Ospedali Azienda ULSS Rovigo
050220/05	Polo Ospedaliera Dell'Est Veronese

Liguria:

070001	Presidio Ospedaliero Unificato Imperiese
070025	Ospedale Galliera
070027	Presidio Ospedaliero Genova Nord - Ospedale Celesta
070031	Presidio Ospedaliero Genova Ponente - Ospedale San Carlo di Voltri

Emilia-Romagna:

080002	Presidio Ospedaliero Val Tidone
080015	Ospedale "S. Maria" Borgo Val di Taro
080053	Presidio Unico Bellaria Maggiore
080068	Presidio Unico Azienda Ausl di Ferrara
080091	Azienda USL di Cesena
080219	Villa Chiara – Casalecchio di Reno (BO)

Toscana:

090601	Presidio Ospedaliero Lunigiana
090615	Presidio Ospedaliero Portoferraio
090623/01	Ospedale S.Andrea di Massa Carrara
090639	Ospedali Riuniti Val di Chiana

Umbria:

100803	Presidio Ospedaliero Unificato ASL 2 Perugia

Marche:

110003	S. Maria della Misericordia - Urbino
110056	Ospedale Generale Prov. Mazzoni - Ascoli Piceno
110921	IRCCS Privato INRCA - Ancona

Lazio:

120055	Ospedale "Luigi Spolverini" - Ariccia
120118	Casa di Cura Villa del Rosario - Roma
120134	Casa di Cura S. Anna - Pomezia
120209	Casa del Sole Clinica "Tommaso Costa" - Formia

Abruzzo:

130005	Presidio Ospedaliero Castel di Sangro

Molise:

140006	Ospedale F. Veneziale - Isernia

Campania:

150010	Presidio Ospedaliero "San Rocco" - Sessa Aurunca (CE)
150140	Presidio Ospedaliero ASL AV-1 Ariano Irpino
150191	Presidio Ospedaliero S.M. delle Grazie - Pozzuoli
150901	Azienda Ospedaliera Cardarelli - Napoli
150906	Azienda Ospedaliera "Rummo" - Benevento

Puglia:

160075	Ospedale "Valle d'Itria" - Martina Franca (TA)
160158	Presidio Ospedaliero "S. Paolo" - Bari
160905	IRCCS Casa Sollievo della Sofferenza - San Giovanni Rotondo

Basilicata:

170011	Presidio Ospedaliero di Matera

Calabria:

180912	Azienda Ospedaliera di Cosenza

Sicilia:

190105	Presidio Ospedaliero Abele Ajello - Mazara del Vallo (TP)
190136	Ospedale Maggiore - Modica
190137	Ospedale Busacca - Scicli
190915	Azienda Ospedaliera Umberto I - Siracusa

Sardegna:

200026	Presidio Ospedaliero Marino - Cagliari
200031	Presidio Ospedaliero "SS. Trinità" - Cagliari

Appendix 5

List of manufacturers

The following manufacturers were cited in the report:

ADVANCED SURGICAL DESIGN & MANUFACTURE LTD. was cited as ASDM

AESCULAP AG was cited as AESCULAP

AMPLITUDE S.A.S was cited as AMPLITUDE

BIOMET INC. was cited as BIOMET

CONSENSUS ORTHOPEDICS INC. was cited as CONSENSUS

CORIN GROUP PLC was cited as CORIN

DEDIENNE SANTÉ was cited as DEDIENNE SANTÉ

DEPUY INC. (A JOHNSON & JOHNSON COMPANY) was cited as DEPUY

ENCORE MEDICAL L.P. was cited as ENCORE

EXACTECH INC. was cited as EXACTECH

F.H. INDUSTRIE was cited as F.H. INDUSTRIE

GLOBAL MANUFACTURING TECHNOLOGY PTY LTD was cited as G.M.T.

HOWMEDICA OSTEONICS CORP. (STRYKER ORTHOPAEDICS) was cited as STRYKER

LIMA LTO S.P.A. was cited as LIMA

MATHYS AG BETTLACH was cited as MATHYS

MEDACTA INTERNATIONAL SA was cited as MEDACTA

PERMEDICA SPA was cited as PERMEDICA

SMITH & NEPHEW INC was cited as SMITH & NEPHEW

SYMBIOS ORTHOPÉDIE SA was cited as SYMBIOS

TORNIER S.A. was cited as TORNIER

TRANSYSTÈME S.A. was cited as TRANSYSTÈME

WALDEMAR LINK GMBH & CO. KG was cited as LINK

WRIGHT MEDICAL TECHNOLOGY, INC. was cited as WRIGHT

ZIMMER INC. was cited as ZIMMER


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Appendix 6

Search strategy

The search strategy illustrated below was conducted starting from the manufacturers and models of prostheses. Therefore, we cannot be sure that all relevant studies have been identified. Readers are requested to notify hta@agenas.it of all studies, that in their opinion, satisfy the criteria for inclusion and do not appear in the list of included or excluded studies.

EMBASE

(device name) and (manufacturer name) and primary total knee replacement (1998-2009)

#1. dual AND ('biomet'/exp OR 'biomet') AND primary AND total AND ('knee'/exp OR 'knee') AND replacement AND [english]/lim AND [humans]/lim AND [1998-2009

#2. (dual AND articular) AND ('biomet'/exp OR 'biomet') AND primary AND total AND ('knee'/exp OR 'knee')AND replacement AND [english]/lim AND [humans]/lim AND [1998-2009]/py

#5. duracon AND primary AND total AND ('knee'/exp OR knee') AND replacement AND [english]/lim AND [humans]/lim AND [1998-2009]/py

#6. (duracon AND ii) AND stryker AND primary AND total AND ('knee'/exp OR 'knee') AND replacement AND [english]/lim AND [humans]/lim AND [1998-2009]/py

#7. (duracon AND ii) AND primary AND total AND ('knee' /exp OR 'knee') AND replacement AND [english]/lim AND [humans]/lim AND [1998-2009]/py

#8. (duracon AND ts) AND stryker AND total AND primary AND replacement AND [english]/lim AND [humans]/lim AND [1998-2009]/py

#9. (ea) AND (j AND & AND j) AND primary AND total AND knee AND replacement AND [english]/lim AND [humans]/lim AND [1998-2009]/py

#10. efdios AND citieffe AND primary AND total AND ('knee'/exp OR 'knee') AND replacement AND [english]/lim AND [humans]/lim AND [1998-2009]/py

#11. eius AND citieffe AND primary AND total AND ('knee '/exp OR 'knee') AND replacement AND [english]/lim AND [humans]/lim AND [1998-2009]/py

#13. eius AND primary AND total AND ('knee'/exp OR 'knee') AND replacement AND [1998-2009]/py

#14. ('e motion') AND 'aesculap bbraun' AND primary AND total AND ('knee'/exp OR 'knee') AND replacement AND [1998-2009]/py

#15. ('e motion') AND aesculap AND primary AND total AND ('knee'/exp OR 'knee') AND replacement AND [1998-2009]/py

#18. aesculap AND primary AND total AND ('knee'/exp OR 'knee') AND replacement AND [1998-2009]/py

#19. endomodel AND eumed AND primary AND total AND ('knee'/exp OR 'knee') AND

replacement AND [1998-2009] /py

#23. endomodel AND medlife AND primary AND total AND ('knee'/exp OR 'knee') AND replacement AND [1998-2009]/py

#24. link AND medlife AND primary AND total AND ('knee' /exp OR 'knee') AND replacement AND [1998-2009]/py

#25. medlife AND primary AND total AND ('knee'/exp OR 'knee') AND replacement AND [1998-2009]/py

#28. link AND medlife AND primary AND total AND knee AND replacement AND [1998-2009]/py

#29. medlife AND endomodel AND primary AND total AND ('knee'/exp OR 'knee') AND replacement AND [1998-2009]/py

#30. evolis AND medacta AND primary AND total AND ('knee'/exp OR 'knee') AND replacement AND [1998-2009]/ py

#31. evolis AND (emme AND a AND medical) AND primary AND total AND ('knee'/exp OR 'knee') AND replacement AND [1998-2009]/py

#32. first AND symbios AND primary AND total AND ('knee'/exp OR 'knee') AND replacement AND [1998-2009]/p y

#33. gemini AND link AND primary AND total AND ('knee'/ exp OR 'knee') AND replacement AND [1998-2009]/py

#34. (('gender'/exp OR 'gender') AND soklutions) AND zimmer AND primary AND total AND ('knee'/exp OR 'knee') AND replacement AND [1998-2009]/py

#35. genesis AND (s AND & AND n) AND primary AND total AND ('knee'/exp OR 'knee') AND replacement AND [1998-2009]/py

#36. genesis AND (s&n) AND primary AND total AND ('knee'/exp OR 'knee') AND replacement AND [1998-2009]/p

#37. genesis AND primary AND total AND ('knee'/exp OR 'knee') AND replacement AND [1998-2009]/py

#44. nephew AND primary AND total AND ('knee'/exp OR 'knee') AND replacement AND [1998-2009]/py

#45. ('genus'/exp OR 'genus') AND adler AND primary AND total AND ('knee'/exp OR 'knee') AND replacement AND [1998-2009]/py

#46. (gks AND jump) AND permedica AND primary AND total AND ('knee'/exp OR 'knee') AND replacement AND [1998-2009]/py

#47. (gks AND prime) AND permedica AND primary AND total AND ('knee'/exp OR 'knee') AND replacement AND [1998-2009]/py

#48. haemicap AND delta AND primary AND total AND ('knee'/exp OR 'knee') AND replacement AND [1998-2009]/py

#49. (hls AND noetos) AND primary AND total AND ('knee'/exp OR 'knee') AND replacement AND [1998-2009]/py

#50. (hls AND noetos) AND tornier AND primary AND total AND ('knee'/exp OR 'knee') AND replacemen AND [1998-2009]/py

#52. innex AND zimmer AND primary AND total AND ('knee' /exp OR 'knee') AND replacement AND [1998-2009]/py

#53. innex AND (center AND ('pulse'/exp OR 'pulse')) AND primary AND total AND ('knee'/exp OR 'knee') AND replacement AND [1998-2009]/py

#54. innex AND (sulzer AND medical) AND primary AND total AND ('knee'/exp OR 'knee') AND replacement AND [1998-2009]/py

#55. innex AND (smith AND & AND nephew) AND primary AND total AND ('knee'/exp OR 'knee') AND replacement AND [1998-2009]/py

#56. journey AND (smith AND & AND nephew) AND primary AND total AND ('knee'/exp OR 'knee') AND replacement AND [1998-2009]/py

#57. jump AND exactech AND primary AND total AND ('knee '/exp OR 'knee') AND replacement AND [1998-2009]/py

#58. keops AND technologie AND transysteme AND primary AND total AND ('knee'/exp OR 'knee') AND replacement AND [1998-2009]/py

#59. kufe AND de AND puy AND primary AND total AND ('knee'/exp OR 'knee') AND replacement AND [1998-2009]/py

#64. lcs AND primary AND total AND ('knee'/exp OR 'knee ') AND replacement AND [humans]/lim AND [1998-2009]/py

#65. lcs AND (comed AND srl) AND primary AND total AND ('knee'/exp OR 'knee') AND replacement AND [1998-2009]/py

#66. (lcs AND apg) AND (de AND puy) AND primary AND total AND ('knee'/exp OR 'knee') AND replacement AND [1998-2009]/py

#67. ('lps'/exp OR 'lps') AND flex AND zimmer AND primary AND total AND ('knee'/exp OR 'knee') AND replacement AND [1998-2009]/py

#68. maior AND primary AND total AND ('knee'/exp OR 'knee') AND replacement AND [1998-2009]/py

#69. ('mba'/exp OR 'mba') AND (('mba'/exp OR 'mba') AND lazio) AND primary AND total AND ('knee'/exp OR 'knee') AND replacement AND [1998-2009]/py

#70. mbt AND (de AND puy) AND primary AND total AND ('knee'/exp OR 'knee') AND replacement AND [1998-2009]/py

#71. (('mg'/exp OR 'mg') AND uni) AND zimmer AND primary AND total AND ('knee'/exp OR 'knee') AND replacement AND [1998-2009]/py

#73. (mini AND one) AND permedica AND primary AND total AND ('knee'/exp OR 'knee') AND replacement AND [1998-2009]/py

#74. multigen AND lima AND primary AND total AND ('knee '/exp OR 'knee') AND replacement AND [1998-2009]/py

#75. (multigen AND plus AND k) AND (lima AND lto AND spa) AND primary AND total AND ('knee'/exp OR 'knee') AND replacement AND [1998-2009]/py

#76. (natural AND ('knee'/exp OR 'knee') AND ii) AND (zimmer) AND primary AND total AND ('knee'/exp OR 'knee') AND replacement AND [1998-2009]/py

#78. nexgen AND AND primary AND total AND ('knee'/exp OR 'knee') AND replacement AND [1998-2009]/py

#84. nexgen AND zimmer AND total AND ('knee'/exp OR 'knee') AND replacement AND [english]/lim AND [humans]/lim AND [1998-2009]/py

#85. (nexgen AND ('cck'/exp OR 'cck')) AND zimmer AND primary AND total AND ('knee'/exp OR 'knee') AND replacement AND [1998-2009]/py

#86. (nexgen AND 'cr flex') AND zimmer AND primary AND total AND ('knee'/exp OR 'knee') AND replacement AND [1998-2009]/py

#87. (nexgen AND ('lps'/exp OR 'lps')) AND zimmer AND primary AND total AND ('knee'/exp OR 'knee') AND replacement AND [1998-2009]/py

#88. (nexgen AND ('lps'/exp OR 'lps') AND flex) AND zimmer AND primary AND total AND ('knee'/exp OR 'knee ') AND replacement AND [1998-2009]/py

#89. (nexgen AND rhk) AND zimmer AND primary AND total AND ('knee'/exp OR 'knee') AND replacement AND [1998-2009]/py

#90. (ngr) AND (how AND osteonics) AND primary AND total AND ('knee'/exp OR 'knee') AND replacement AND [1998-2009]/py

#91. (noiles AND minge) AND (de AND puy) AND primary AND total AND ('knee'/exp OR 'knee') AND replacement AND [1998-2009]/py

#92. (optetrak) AND (exacteh) AND primary AND total AND ('knee'/exp OR 'knee') AND replacement AND [1998-2009]/py

#95. optetrak AND primary AND total AND ('knee'/exp OR 'knee') AND replacement AND [1998-2009]/py

#98. oxford AND primary AND total AND ('knee'/exp OR 'knee') AND replacement AND [english]/lim AND [humans]/lim AND [1998-2009]/py

#99. (oxford AND iii) AND ('biomet'/exp OR 'biomet') AND primary AND total AND ('knee'/exp OR 'knee') AND replacement AND [1998-2009]/py

#100. (oxinium) AND s AND n AND primary AND total AND knee AND replacement AND [1998-2009]/py

#101. (pfc AND sigma) AND j&j AND primary AND total AND knee AND replacement AND [1998-2009]/py

#103. (pfc AND sigma) AND primary AND total AND knee AND replacement AND [humans]/lim AND [1998-2009]/py

#104. (pfc AND sigma) AND (de AND puy) AND primary AND t 5 27 May 2009

otal AND ('knee'/exp OR 'knee') AND replacement AND [1998-2009]/py

#105. (pfc AND sigma) AND (de AND puy) AND primary AND total AND ('knee'/exp OR 'knee') AND replacement AND [humans]/lim AND [1998-2009]/py

#106. ('preservation'/exp OR 'preservation') AND (de AND puy) AND primary AND total AND ('knee'/exp OR 'knee') AND replacement AND [humans]/lim AND [1998-2009]/py

#108. (prime) AND (exatech) AND primary AND total AND (' knee'/exp OR 'knee') AND replacement AND [humans]/lim AND [1998-2009]/py

#109. profix AND (smith AND & AND nephew) AND primary AND total AND ('knee'/exp OR 'knee') AND replacement AND [1998-2009]/py

#110. ptco AND (advancor) AND primary AND total AND ('knee'/exp OR 'knee') AND replacement AND [1998-2009]/py

#111. profix AND primary AND total AND ('knee'/exp OR 'knee') AND replacement AND [1998-2009]/py

#112. rhk AND ('biomet'/exp OR 'biomet') AND primary AND total AND ('knee'/exp OR 'knee') AND replacement AND [1998-2009]/py

#113. rocc AND ('biomet'/exp OR 'biomet') AND primary AND total AND ('knee'/exp OR 'knee') AND replacement AND [1998-2009]/py

#114. rotaglide AND mida AND primary AND total AND ('knee'/exp OR 'knee') AND replacement AND [1998-2009]/ py

#116. rotaglide AND primary AND total AND ('knee'/exp OR 'knee') AND replacement AND [humans]/lim AND [1998-2009]/py

#118. rotaglide AND (corin) AND (fluit) AND primary AND total AND ('knee'/exp OR 'knee') AND replacement AND [english]/lim AND [humans]/lim AND [1998-2009]/py

#119. ('rt plus') AND (plus AND ('orthopedics'/exp OR 'orthopedics')) AND primary AND total AND ('knee'/exp OR 'knee') AND replacement AND [english]/lim AND [humans]/lim AND [1998-2009]/py

#120. score AND amplitude AND adler AND primary AND total AND knee AND replacement AND [1998-2009]/py

#123. amplitude AND primary AND total AND ('knee'/exp OR 'knee') AND replacement AND [1998-2009]/py

#124. (score AND rev) AND mida AND primary AND total AND ('knee'/exp OR 'knee') AND replacement AND [1998-2009]/py

#125. scororpio AND stryker AND primary AND total AND ('knee'/exp OR 'knee') AND replacement AND [1998-2009]/py

#126. scorpio AND stryker AND primary AND total AND ('knee'/exp OR 'knee') AND replacement AND [1998-2009]/py

#127. scorpio AND primary AND total AND ('knee'/exp OR ' knee') AND replacement AND [1998-2009]/py

#130. scorpio AND total AND ('knee'/exp OR 'knee') AND replacement AND [english]/lim AND [humans]/lim AND [1998-2009]/py

#131. stryker AND scorpio AND primary AND total AND ('knee'/exp OR 'knee') AND replacement AND [1998-2009]/py

#132. stryker AND primary AND total AND ('knee'/exp OR `knee') AND replacement AND [1998-2009]/py

#133. stryker AND primary AND total AND ('knee'/exp OR ' knee') AND replacement AND [humans]/lim AND [1998-2009]/py

#134. stryker AND primary AND total AND ('knee'/exp OR 'knee') AND replacement AND [english]/lim AND [humans]/lim AND [1998-2009]/py

#142. scorpio AND stryker AND total AND ('knee'/exp OR ' knee') AND replacement AND [english]/lim AND [humans]/lim AND [1998-2009]/py

#143. scorpio AND (how AND osteonics) AND primary AND total AND ('knee'/exp OR 'knee') AND replacement AND [1998-2009]/py

#144. (scorpio AND ('cr'/exp OR 'cr')) AND (stryker) AND primary AND total AND ('knee'/exp OR 'knee') AND replacement AND [1998-2009]/py

#145. (scorpio AND nrg) AND (stryker) AND primary AND total AND ('knee'/exp OR 'knee') AND replacement AND [1998-2009]/py

#146. (serie AND 7000) AND (how AND osteonics) AND primary AND total AND ('knee'/exp OR 'knee') AND replacement AND [1998-2009]/py

#147. (sigma AND ('rpf'/exp OR 'rpf') AND hi) AND (de AND puy) AND primary AND total AND ('knee'/exp OR 'knee') AND replacement AND [1998-2009]/py

#148. sleeve AND (de AND puy) AND primary AND total AND ('knee'/exp OR 'knee') AND replacement AND [1998-2009]/py

#149. sleeve AND primary AND total AND ('knee'/exp OR 'knee') AND replacement AND [1998-2009]/py

#150. (sol AND cem) AND zimmer AND primary AND total ('knee'/exp OR 'knee') AND replacement AND [1998-2009]/py

#151. (spacer AND k) AND orthofix AND primary AND total AND ('knee'/exp OR 'knee') AND replacement AND [1998-2009]/py

#152. spacer AND k AND orthofix AND primary AND total AND ('knee'/exp OR 'knee') AND replacement AND [1998-2009]/py

#156. 's rom' AND primary AND total AND ('knee'/exp OR 'knee') AND replacement AND [1998-2009]/py

#157. 'tc plus' AND (plus AND ('orthopedics'/exp OR 'orthopedics')) AND primary AND total AND ('knee'/exp OR 'knee') AND replacement AND [1998-2009]/py

#158. tl3 AND (de AND puy) AND primary AND total AND ('knee'/exp OR 'knee') AND replacement AND [1998-2009]/py

#161. tray AND primary AND total AND ('knee'/exp OR 'knee') AND replacement AND [humans]/lim AND [1998-2009]/py

#162. ('triathlon'/exp OR 'triathlon') AND stryker AND primary AND total AND ('knee'/exp OR 'knee') AND replacement AND [1998-2009]/py

#163. (uni AND genesis) AND (smith AND & AND nephew) AND primary AND total AND ('knee'/exp OR 'knee') AND replacement AND [1998-2009]/py

#164. (uni AND ('knee'/exp OR 'knee')) AND (de AND puy) AND primary AND total AND ('knee'/exp OR 'knee') AND replacement AND [1998-2009]/py

#165. (vanguard) AND ('biomet'/exp OR 'biomet') AND primary AND total AND ('knee'/exp OR 'knee') AND replacement AND [1998-2009]/py

#166. (vanguard AND ps) AND ('biomet'/exp OR 'biomet') AND primary AND total AND ('knee'/exp OR 'knee') AND replacement AND [1998-2009]/py

#167. ('vitallium'/exp OR 'vitallium') AND (stryker) AND primary AND total AND ('knee'/exp OR 'knee') AND replacement AND [1998-2009]/py

#182. agc AND ('biomet'/exp OR 'biomet') AND total AND ('knee'/exp OR 'knee') AND replacement AND [english]/lim AND [humans]/lim AND [1998-2009]/py

#183. advance AND wright AND primary AND total AND ('knee'/exp OR 'knee') AND replacement AND [1998-2009]/ py

#184. advance AND primary AND total AND ('knee'/exp OR 'knee') AND replacement AND [1998-2009]/py

#185. academia AND (fm AND ('orthopedics'/exp OR 'orthopedics')) AND primary AND total AND ('knee'/exp OR knee') AND replacement AND [1998-2009]/py

#186. academia AND primary AND total AND ('knee'/exp OR 'knee') AND replacement AND [1998-2009]/py

#187. accuris AND (smith AND & AND nephew) AND primary AND total AND ('knee'/exp OR 'knee') AND replacement AND [1998-2009]/py

#188. (abc AND da AND 2000) AND ('biomet'/exp OR 'biomet') AND primary AND total AND ('knee'/exp OR 'knee') AND replacement AND [1998-2009]/py

#189. (3dknee) AND (encore AND djo AND surgical) AND primary AND total AND ('knee'/exp OR 'knee') AND replacement AND [1998-2009]/py

#190. (agc AND v2) AND ('biomet'/exp OR 'biomet') AND primary AND total AND ('knee'/exp OR 'knee') AND replacement AND [1998-2009]/py

#191. (allegretto) AND (zimmer) AND primary AND total AND ('knee'/exp OR 'knee') AND replacement AND [1998 -2009]/py

#192. (amc AND mkii) AND (corin AND fluit) AND primary AND total AND ('knee'/exp OR 'knee') AND replacement AND [1998-2009]/py

#193. (amplitude) AND (adler) AND primary AND total AND ('knee'/exp OR 'knee') AND replacement AND [1998-2009]/py

#194. (amplitude) AND primary AND total AND ('knee'/exp OR 'knee') AND replacement AND [1998-2009]/py

#197. avon AND primary AND total AND ('knee'/exp OR 'knee') AND replacement AND [humans]/lim AND [1998-2009]/py

#198. (('balan'/exp OR 'balan') AND sys) AND myrmex AND primary AND total AND ('knee'/exp OR 'knee') AND replacement AND [humans]/lim AND [1998-2009]/py

#199. (balansis) AND myrmex AND primary AND total AND ('knee'/exp OR 'knee') AND replacement AND [humans]/lim AND [1998-2009]/py

#200. (bsn AND medical) AND myrmex AND primary AND total AND ('knee'/exp OR 'knee') AND replacement AND [humans]/lim AND [1998-2009]/py

#201. ('butterfly'/exp OR 'butterfly') AND permedica AND primary AND total AND ('knee'/exp OR 'knee') AND replacement AND [humans]/lim AND [1998-2009]/py

#202. chart AND stick AND (how AND osteonics) AND primar y AND total AND ('knee'/exp OR 'knee') AND replacement AND [humans]/lim AND [1998-2009]/py

#203. cinetique AND medacta AND primary AND total AND (' knee'/exp OR 'knee') AND replacement AND [humans]/ lim AND [1998-2009]/py

#204. columbus AND aesculap AND primary AND total AND (' knee'/exp OR 'knee') AND replacement AND [humans]/ lim AND [1998-2009]/py

#205. columbus AND aesculap AND primary AND total AND (' knee'/exp OR 'knee') AND replacement AND [1998-2009]/py

#209. aesculap AND primary AND total AND ('knee'/exp OR 'knee') AND replacement AND [english]/lim AND [humans]/lim AND [1998-2009]/py

#213. ('consensus'/exp OR 'consensus') AND primary AND total AND ('knee'/exp OR 'knee') AND replacement AND [abstracts]/lim AND [1998-2009]/py

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(device name) and (manufacturer name) and primary total knee replacement (1998-2009)
Select 20 document(s)

Select 2 document(s)

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Select 1 document(s)

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Select 1 document(s)

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Select 4 document(s)

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Search ("1998-01-01"[Publication Date] : "2009-04-30"[Publication Date]) AND stryker and scorpio and primary total knee replacement)

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Search ("1998-01-01"[Publication Date] : "2009-04-30"[Publication Date]) AND "nexgen oxinium" and zimmer and primary total knee replacement)

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Search ("1998-01-01"[Publication Date] : "2009-04-30"[Publication Date]) AND nexgen and zimmer and primary total knee replacement)

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Search ("1998-01-01"[Publication Date] : "2009-04-30"[Publication Date]) AND RT-Plus and "smith & nephew" and primary total knee replacement)

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ing" and "smith & nephew" and primary total knee replacement)

Search ("1998-01-01"[Publication Date] : "2009-04-30"[Publication Date]) AND "smith & nephew" and legion and primary total knee replacement)

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Search ("1998-01-01"[Publication Date] : "2009-04-30"[Publication Date]) AND cinetique and medacta and primary total knee replacement)

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Search	("1998-01-01"[Publication Date] : "2009-04-30"[Publication Date]) AND (MBT and depuy and primary total knee replacement)
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Search	("1998-01-01"[Publication Date] : "2009-04-30"[Publication Date]) AND (Vanguard and biomet and primary total knee replacement)
Search	("1998-01-01"[Publication Date] : "2009-04-30"[Publication Date]) AND (ROCC and biomet and primary total knee replacement)
Search	("1998-01-01"[Publication Date] : "2009-04-30"[Publication Date]) AND (RHK and biomet and primary total knee replacement)
Search	("1998-01-01"[Publication Date] : "2009-04-30"[Publication Date]) AND (score and amplitude and primary total knee replacement)
Search	("1998-01-01"[Publication Date] : "2009-04-30"[Publication Date]) AND (Emotion and aesculap and primary total knee replacement)
Search	("1998-01-01"[Publication Date] : "2009-04-30"[Publication Date]) AND (E.motion and aesculap and primary total knee replacement)

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"Total knee replacement" and (replacement or prosthesis or implantation or arthroplasty) (1998-2009)


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Appendix 7

Data extraction form for single studies

General description

NB: Do not leave blank spaces. If there is no answer to the question write NR (not reported) or NA (not applicable)

Study ID:

Published [Y/N]:

Date of publication:

Period of the study [from/to]:

Country of study:

Form of publication [abstract/full paper]:

Biblio ref.:

Type of funder [Government, mixed, private, industry, unfunded, undeclared/unknown]:

PubMed abstract:

Methods description

Rationale:

Objective:

Measured outcomes:

Groups of the study
- Group 1:
- Group 2:

Population:
Total number of patients enrolled in the study: (knees)
Patient excluded from the study: (knees)
Total number of participants: (knees)

Number of participants for each group
Group 1:
Group 2:

Age at surgery (mean ± SD; (range)) [years]:
Group 1:
Group 2:

Gender [num. M / num. F]:
Group 1:
Group 2:

Clinical follow-up (mean ± SD; (range)) [years]:
Group 1:
Group 2:

Other follow-up (e.g. radiological): Mean ± SD; (range) [years]:
Group 1:
Group 2:

Type of implant [cemented, cementless, hybrid]
Group 1:
Group 2:

Name of device
Group 1:
Group 2:

Further characteristics:
Group 1:
Group 2:

Common characteristics:

Manufacturer
- Group 1:
- Group 2:

Setting [general hospital/specialised institute]:

Results description

Synthesis of the results:

Device related complications:

Wear	[ ]	Revised [ ]
Loosening	[ ]	Revised [ ]
Dislocation	[ ]	Revised [ ]
Infection (sepsis)	[ ]	Revised [ ]
Osteolysis	[ ]	Revised [ ]
Other (to specify)	[ ]	Revised [ ]

Number of implants subjected to revision during the study:

Conclusions description

Conclusions:

Assessment of generalisability of results:

Bottom line:


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Appendix 8

Data extraction form for registry-based studies

Knee system	Total	Number of revisions	Male/Female	Mean age (range)	Osteoarthritis (%)	Survival rate at 5 years [%] (95% CI)


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Appendix 9

Quality assessment tool

Checklist for the quality assessment of single studies based on Total Knee replacement – Evidence report N° 86, AHRQ Pubblication No. 04-E006-2, December 2003.

Study ID:			
Number	**Element**	**Y/N/UC**	**Notes**
1	Study question clearly focused		
2	Description of study population		
3	Clear definition of intervention		
4	Primary/secondary outcome defined		
5	Statistical analysis		
6	Conclusion supported by results		
7	Single versus Multi-site study		
8	Patients evaluated with radiographs for outcome		
9	Comorbidities mentioned		
10	Comorbidities incorporated in the analyses		
11	Death rates recorded		
12	Measurement scale adopted		
13	Declaration of conflict of interest		

Notes: Y: Yes N: No UC: Unclear


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Appendix 10

List of excluded studies with reasons for exclusion

Studies excluded for inappropriate design of study:

Anderson JA, MacDessi SJ, Della Valle AG. Spontaneous, recurrent dislodgment of the polyethylene tibial insert after total knee arthroplasty: A case report. J. Bone Jt. Surg. Ser. A 2007; 89(2):404-7.

Buechel FF. Mobile-bearing knee arthroplasty: Rotation is our salvation! J. Arthroplasty 2004; 19(4 SUPPL. 1):27-30.

Crova M, Cenna E, Olivero C. Rotating knee prosthesis. Surface or hinge replacement? Orthopade 2000; 29 Suppl 1(-):S43-4.

Kane R L, Saleh K J, Wilt T J et al. Total knee replacement (Structured abstract). Rockville: Agency for Healthcare Research and Quality (AHRQ) 2003.

Keating EM, Meding JB, Faris PM, Ritter MA. Long-term followup of nonmodular total knee replacements. Clin. Orthop. Relat. Res. 2002; -(404):34-9.

Ma H-M, Lu Y-C, Kwok T-G, Ho FY, Huang C-Y, Huang C-H. The effect of the design of the femoral component on the conformity of the patellofemoral joint in total knee replacement. J. Bone Jt. Surg. Ser. B 2007; 89(3):408-12.

Mihalko W, Fishkin Z, Krakow K. Patellofemoral overstuff and its relationship to flexion after total knee arthroplasty. Clin. Orthop. Relat. Res. 2006; -(449):283-7.

Newman JH, Ackroyd CE, Shah NA. Unicompartmental or total knee replacement? Five-year results of a prospective, randomised trial of 102 osteoarthritic knees with unicompartmental arthritis. J Bone Joint Surg Br 1998; 80(5):862-5.

Ontario Ministry of Health and Long-Term Care. Total knee replacement (Structured abstract). Toronto: Medical Advisory Secretariat, Ontario Ministry of Health and Long-Term Care (MAS) 2005; 51.

Rawlinson JJ, Furman BD, Li S, Wright TM, Bartel DL. Retrieval, experimental, and computational assessment of the performance of total knee replacements. J. Orthop. Res. 2006; 24(7):1384-94.

Studies excluded for irrelevant topic:

Barton TM, White SP, Mintowt-Czyz W, Porteous AJ, Newman JH. A comparison of patient based outcome following knee arthrodesis for failed total knee arthroplasty and revision knee arthroplasty. Knee 2008; 15(2):98-100.

Berend ME, Ritter MA, Keating EM, Faris PM, Crites BM. The failure of all-polyethylene patellar components in total knee replacement. Clin. Orthop. Relat. Res. 2001; -(388):105-11.

Carlsson A, Björkman A, Besjakov J, Onsten I. Cemented tibial component fixation performs better than cementless fixation: a randomized radiostereometric study comparing porous-coated, hydroxyapatite-coated and cemented tibial components over 5 years. Acta Orthopaedica 2005; 76(3):362-9.

Hall J, Copp SN, Adelson WS, D'Lima DD, Colwell CW. Extensor mechanism function in single-radius vs multiradius femoral components for total knee arthroplasty. J Arthroplasty 2008; 23(2):216-9.

Huang C-H, Ho F-Y, Ma H-M et al. Particle size and morphology of UHMWPE wear debris in failed total knee arthroplasties - A comparison between mobile bearing and fixed bearing knees. J. Orthop. Res. 2002; 20(5):1038-41.

Jacobs Wilco, Anderson Patricia G, van Limbeek Jacques, Wymenga Ate AB. Mobile bearing vs fixed bearing prostheses for total knee arthroplasty for post-operative functional status in patients with osteoarthritis and rheumatoid arthritis. Cochrane Database of Systematic Reviews: Reviews 2001 Issue 2 John Wiley & Sons, Ltd Chichester, UK DOI: 10.1002/14651858.CD003130.Pub2 2001; (2).

Jacobs Wilco, Clement Darren J, Wymenga Ate AB. Retention Versus Sacrifice of the Posterior Cruciate Ligament in Total Knee Replacement for Treatment of Osteoarthritis and Rheumatoid Arthritis. Cochrane Database of Systematic Reviews: Reviews 2005 Issue 4 John Wiley & Sons, Ltd Chichester, UK DOI: 10.1002/14651858.CD004803.Pub2 2005; (4).

Johnson S, Jones P, Newman JH. The survivorship and results of total knee replacements converted from unicompartimental knee replacements. Knee 2007; 14(2):154-7.

Muller W, Wirz D. The patella in total knee replacement: does it matter? 750 LCS total knee replacements without resurfacing of the patella. Knee Surg Sports Traumatol Arthrosc 2001; 9 Suppl 1(-):S24-6.

Sterling RS. Supracondylar femur fractures after total knee arthroplasty. Curr. Opin. Orthop. 2003; 14(1):34-40.

Stockl B, Nogler M, Rosiek R, Fischer M, Krismer M, Kessler O. Navigation improves accuracy of rotational alignment in total knee arthroplasty. Clin. Orthop. Relat. Res. 2004; -(426):180-6.

Thompson NW, Wilson DS, Cran GW, Beverland DE, Stiehl JB. Dislocation of the rotating platform after low contact stress total knee arthroplasty. Clin. Orthop. Relat. Res. 2004; -(425):207-11.

Studies excluded for short follow-up and patients age:

Abbas D, Gunn RS. Medium-term results of the Scorpio Total Knee Replacement. Knee 2006; 13(4):307-11.

Baker PN, Khaw FM, Kirk LM, Esler CN, Gregg PJ. A randomised controlled trial of cemented versus cementless press-fit condylar total knee replacement: 15-year survival analysis. J Bone Joint Surg Br 2007; 89(12):1608-14.

Buechel Sr. FF. Long-term followup after mobile-bearing total knee replacement. Clin. Orthop. Relat. Res. 2002; -(404):40-50.

Callaghan JJ, Squire MW, Goetz DD, Sullivan PM, Johnston RC. Cemented rotating-platform total knee replacement. A nine to twelve-year follow-up study. J. Bone Jt. Surg. Ser. A 2000; 82(5):705-11.

Clayton RAE, Amin AK, Gaston MS, Brenkel IJ. Five-year results of the Sigma total knee arthroplasty. Knee 2006; 13(5):359-64.

Cooke C, Walter WK, Zicat B. Tibial fixation without screws in cementless total knee arthroplasty. J. Arthroplasty 2006; 21(2):237-41.

Crites BM, Berend ME, Ritter MA. Metal-backed patellar components: A brief report on 10-year survival. Clin. Orthop. Relat. Res. 2001; -(388):103-4.

Findlay IA, Bowman NK, Miles K, East DJ, Apthorp HD, Butler-Manuel A. The AGC total knee replacement-cemented versus cementless hydroxyapatite fixation. J. Bone Jt. Surg. Ser. B 2008; -(SUPPL.):JUNE.

Gandhi R, Tso P, Davey JR, Mahomed NN. High-flexion implants in primary total knee arthroplasty: A meta-analysis. Knee 2009; 16(1):14-7.

Harato K, Bourne RB, Victor J, Snyder M, Hart J, Ries MD. Midterm comparison of posterior cruciate-retaining versus -substituting total knee arthroplasty using the Genesis II prosthesis. A multicenter prospective randomized clinical trial. The Knee 2008; 15(3):217-21.

Huddleston JI, Scott RD, Wimberley DW. Determination of neutral tibial rotational alignment in rotating platform TKA. Clin. Orthop. Relat. Res. 2005; -(440):101-6.

Ishii Y, Matsuda Y, Sakata S, Onda N, Omori G. Primary total knee arthroplasty using the Genesis I total knee prosthesis: a 5- to 10-year follow-up study. The Knee 2005; 12(5):341-5.

Jordan LR, Sorrells RB, Jordan LC, Olivo JL. The long-term results of a metal-backed mobile bearing patella. Clin. Orthop. Relat. Res. 2005; -(436):111-8.

Khaw FM, Kirk LM, Morris RW, Gregg PJ. A randomised, controlled trial of cemented versus cementless press-fit condylar total knee replacement. Ten-year survival analysis. J Bone Joint Surg Br 2002; 84(5):658-66.

Kim YH, Kim DY, Kim JS. Simultaneous mobile- and fixed-bearing total knee replacement in the same patients. A prospective comparison of mid-term outcomes using a similar design of prosthesis. J Bone Joint Surg Br 2007; 89(7):904-10.

Kim YH, Kim JS. Comparison of anterior-posterior-glide and rotating-platform low contact stress mobile-bearing total knee arthroplasties. The Journal of Bone and Joint Surgery. American Volume 2004; 86-A(6):1239-47.

Kolisek FR, Barnes CL. Scorpio Posterior-Stabilized Knee System: 5-Year Clinical and Functional Results. J. Arthroplasty 2006; 21(8):1187-92.

Laskin RS, Maruyama Y, Villaneuva M, Bourne R. Deep-dish congruent tibial component use in total knee arthroplasty: a randomized prospective study. Clin Orthop 2000; (380):36-44.

Laskin RS. The effect of a high-flex implant on postoperative flexion after primary total knee arthroplasty. Orthopedics 2007; 30(8 SUPPL.):86-8.

Meding JB, Ritter MA, Faris PM. Total knee arthroplasty with 4.4 mm of Tibial polyethylene: 10-Year followup. Clin. Orthop. Relat. Res. 2001; -(388):112-7.

Morgan M, Brooks S, Nelson RA. Total Knee Arthroplasty in Young Active Patients Using a Highly Congruent Fully Mobile Prosthesis. J. Arthroplasty 2007; 22(4):525-30.

Muller SD, Deehan DJ, Holland JP et al. Should we reconsider all-polyethylene tibial implants in total knee replacement? J. Bone Jt. Surg. Ser. B 2006; 88(12):1596-602.

Murray DW, Frost SJD. Pain in the assessment of total knee replacement. J. Bone Jt. Surg. Ser. B 1998; 80(3):426-31.

Najibi S, Iorio R, Surdam JW, Whang W, Appleby D, Healy WL. All-polyethylene and metal-backed tibial components in total knee arthroplasty: A matched pair analysis of functional outcome. J. Arthroplasty 2003; 18(7 SUPPL. 1):9-15.

Noble PC, Conditt MA, Thompson MT et al. Extraarticular Abrasive Wear in Cemented and Cementless Total Knee Arthroplasty. Clin. Orthop. Relat. Res. 2003; -(416):120-8.

Pomeroy DL, Schaper LA, Badenhausen WE et al. Results of all-polyethylene tibial components as a cost-saving technique. Clin. Orthop. Relat. Res. 2000; -(380):140-3.

Robinson RP. Five-year follow-up of primary optetrak posterior stabilized total knee arthroplasties in osteoarthritis. J. Arthroplasty 2005; 20(7):927-31.

Sorrells RB, Capps SG. Clinical results of primary low contact stress cementless total knee arthroplasty. Orthopedics 2006; 29(9 SUPLL.):S42-S44.

Sorrells RB, Voorhorst PE, Murphy JA, Bauschka MP, Greenwald AS. Uncemented rotating-platform total knee replacement: A five to twelve-year follow-up study. J. Bone Jt. Surg. Ser. A 2004; 86(10):2156-62.

Thomas A, Rojer D, Imrie S, Goodman SB. Cemented total knee arthroplasty in patients with juvenile rheumatoid arthritis. Clin. Orthop. Relat. Res. 2005; -(433):140-6.

Wilson CJ, Fitzgerald B, Tait GR. Five year review of the Rotaglide total knee Arthroplasty. Knee 2003; 10(2):167-71.

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Appendix 11

List of included studies

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Acronyms and abbreviations

Agenas	Agenzia nazionale per i servizi sanitari regionali
AOAJRR	Australian Orthopaedic Association National Joint Replacement Register
ASA class	ASA stands for American Society of Anesthesiologists. It is a six category physical status classification system for assessing a patient before surgery.
Assobiomedica	Association of producers and distributors of medical devices
AU	Australia
BMI	Body Mass Index
CI	Confidence interval
CR	Cruciate retaining
CUD	Commissione Unica Dispositivi medici, Ministerial Committee on Medical Devices
DRG	Diagnosis related group
EAR	European Arthroplasty Register
EFORT	European Federation of National Associations of Orthopaedics and Traumatology
ER	Emilia-Romagna
ICD-9-CM	International Classification of Diseases, Ninth Revision, Clinical Modification
ICER	Incremental cost-effectiveness ratio
INHS	Italian National Health Service
IRCCS	Clinical research centres
ISS	Istituto Superiore di Sanità
K-M	Kaplan-Meier
Knee System	Total knee prosthesis
MLHSP	Ministry of Labour, Health and Social Policy
NZJRR	New Zealand Joint Replacement Register
OA	Osteoarthritis
P.A.	Provincie Autonome, regional equivalent
PMMA	Polymethylmethacrylate
PS	Posterior stabilised
RA	Reumathoid arthritis
RCT	Randomised Controlled Trial

RDM	Repertorio nazionale dei dispositivi medici (national inventory of medical devices)
RIPO	Registro dell'Implantologia Protesica Ortopedica (Register of the Orthopaedic Prosthetic Implants)
SDO	Scheda di dimissione ospedaliera (hospital discharge record)
TKA	Total knee arthroplsty
TKR	Total knee replacement
UKR	Unicompartmental knee replacement