# Cost-effectiveness of timely *versus* delayed primary total hip replacement in Germany: A social health insurance perspective

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## Abstract

Without clinical guideline on the optimal timing for primary total hip replacement (THR), patients often receive the operation with delay. Delaying THR may negatively affect long-term health-related quality of life, but its economic effects are unclear. We evaluated the costs and health benefits of timely primary THR for functionally independent adult patients with end-stage osteoarthritis (OA) compared to non-surgical therapy followed by THR after progression to functional dependence (delayed THR), and non-surgical therapy alone (Medical Therapy), from a German Social Health Insurance (SHI) perspective. Data from hip arthroplasty registers and a systematic review of the published literature were used to populate a tunnel-state modified Markov lifetime model of OA treatment in Germany. A 5% annual discount rate was applied to costs (2013 prices) and health outcomes (Quality Adjusted Life Years, QALY). The expected future average cost of timely THR, delayed THR and medical therapy in women at age 55 were €27,474, €27,083 and €28,263, and QALYs were 20.7, 16.7, and 10.3, respectively. QALY differences were entirely due to health-related quality of life differences. The discounted cost per QALY gained by timely over delayed (median delay of 11 years) THR was €1270 and €1338 in women treated at age 55 and age 65, respectively, and slightly higher than this for men. Timely THR is cost-effective, generating large quality of life benefits for patients at low additional cost to the SHI. With declining healthcare budgets, research is needed to identify the characteristics of those able to benefit the most from timely THR.

## Introduction

Besides patient preference, access to primary total hip replacement (THR) for patients with severe hip osteoarthritis (OA) is determined by clinicians' perceptions of risks of surgical complications and implant failure.[1-3] In England, budgetary pressures are also leading to increased rationing.[4] While some patients may benefit from delaying surgery,[5] on average patients aged 50 and older may be better off by undergoing surgery as soon as becoming eligible for THR (timely THR) and while still functionally independent.[3] It is unclear, however, who should be offered THR, and guidelines only state that eligible patients are those that have chronic pain that is not controlled by medication and non-medical therapies.[2]

Delaying surgery has the two-fold advantage of reducing the risk of revision occurrence, and increasing the expected health improvement, since THR produces larger quality of life gains in patients with more severe disease.[6] However, it imposes quality of life losses on patients' health during the delay, and inferior quality of life outcomes post-operatively relative to timely surgery.[3,7]

Despite concerns that 14% of patients do not report improvement after THR,[8-11] there is increasing utilization of hip replacement, driven by clinical need,[12] and demographic change.[13] While there is evidence on the potential cost-effectiveness of timely THR,[3,14] no evidence on this question exists for Germany.

This study sought to evaluate cost-effectiveness of primary hip replacement in Germany. It compared three treatment options for a patient with end-stage osteoarthritis: timely total primary hip replacement, delayed total hip replacement, and non-surgical therapy from the perspective of the statutory health insurer.

## Materials and Methods

### Decision analytic model

A Markov model previously published[3] was adapted to Germany. Its structure is illustrated in Figure 1, depicting a cohort of functionally independent [American College of Rheumatologists (ACR) class III] patients with severe OA undergoing primary THR surgery. The alternative, to remain under non-surgical therapy with non-steroidal anti-inflammatory drugs (NSAIDs), involves two mutually exclusive options, namely, to delay therapy until disease progression to functional dependency (ACR class IV) or a lifetime without operation. Conditional on the choice of treatment and baseline patient age the model represents a series of annual contingent transitions to different health states until death. In each cycle the patient incurs costs and accrues value (utility) from health-related quality of life (HRQoL) in the state occupied.

Following primary THR, the patient may die as a result of surgery or survive the

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Contributions: RMM designed the study, reviewed the costs and effectiveness studies, developed and populated with data the decision analysis model, and wrote the first draft of the manuscript. LKW designed, conducted and wrote the methods of the systematic electronic bibliographic search and contributed to writing the manuscript. RT contributed to writing the Introduction and Discussion sections of the manuscript. MJ contributed to writing the manuscript and reviewed the scientific content of the manuscript. All authors read and approved the final manuscript.

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operation (Success state). The following year a survivor may experience implant failure, and therefore need for revision operation, or remain in the Success state. The former eventuality is associated with a temporary (1-year period) deterioration in HRQoL, and increase in healthcare costs while awaiting revision surgery (Figure 1B).

Under the non-surgical option, the patient is in the initial state before progression (*i.e.* in ACR class III) or post progression to functional dependency (*i.e.* in ACR IV) or dead. Disease progression involves increased healthcare resource consumption and lower utility due to greater limitations on physical function, less mobility and more severe pain (Figure 1A).

Under Delayed primary THR the patient is referred to THR upon disease progression to functional dependence. Once referred to THR the patient faces the same risk of death due to surgery as patients of the same age undergoing surgery in the first place, although different gains in utility are accrued, since utility would have declined while waiting and greater gains are expected with surgery at lower pre-operative utility; the level of utility achieved after delayed surgery is nevertheless lower than that after immediate THR[15] (Figure 1).

The model defines cohorts by sex and age with distinct revision risk profiles. Health value is measured as Quality-Adjusted Life Years (QALYs), whereby each annual cycle is assigned a utility payoff, a preference based valuation of HRQoL in the occupied health state, on a scale ranging from a negative number (for states worse than death), including zero (states equivalent to death), to 1 (representing full health). Under each treatment option, total health value and costs are the sum of QALYs and costs over the modelled lifespan of the cohort up to a maximum age of 100, and are discounted at an annual rate of 5%.[16]

A review of the research literature on German settings was conducted to populate model parameters on implant survival (rates of implant revision operations by age and sex groups) for primary and revision hip replacement operations, distribution of type of revision operations (aseptic loosening, sepsis and other), surgical complications, NSAID medication use by OA severity, rate of OA disease progression under medical therapy. The review also sought to identify costs of primary THR, revision hip replacement (RHR) and non-surgical therapy and utilities for the states of post-operative success, revision, successful revision, functionally dependent OA and functionally independent OA.

## Literature review: identification of studies

PRISMA principles were employed for reviewing the existing literature.[17,18] Searches were conducted in Medline and Embase (via OVID), Cinahl (via EBSCO) and Cochrane Library (including Cochrane Systematic Reviews, the Database of Abstracts of Reviews of Effects (DARE), the National Health System Economic Evaluation Database (NHS EED), and Health Technology Assessment databases) and ISI Web of Science, from inception to end of May 2014. Search terms were constructed using free text, MeSH and thesaurus terms (Appendix I). After deduplication of bibliographic records, titles and abstracts were screened independently by two reviewers. The full-text of potential relevant articles was obtained.

Articles were considered if they were written in English or German. Articles reporting information on: i) health outcomes; ii) healthcare costs of prostheses and THR surgery, complications, rehabilitation, follow-up, revision, and non-surgical management; iii) health state utilities; and iv) indirect costs of OA disease or its treatment were included.

Health outcome studies had to report on management of OA patients in routine practice. Evidence related to specific devices or surgical techniques was not considered. Studies with THR patient cohorts <100 or with follow-ups<10 years were excluded. Studies on healthcare and productivity costs other than in German population were excluded. Studies on health state utility were included if reporting outcomes for OA patients at different levels of disease severity, as defined by Harris Hip Score (HSS) class or equivalent measures.

Details of the included study type, population, year, summary outcome measures reported were extracted by one reviewer, and verified by a second reviewer.

All included studies were assessed for methodological quality according to Cochrane and Centre for Reviews and Dissemination (CRD) guidance criteria for conducting systematic reviews,[19] adapted to our aim to populate an economic model. The overall quality of the studies and data were synthesized through a narrative review.

## Literature review: results

The electronic search produced 2,865

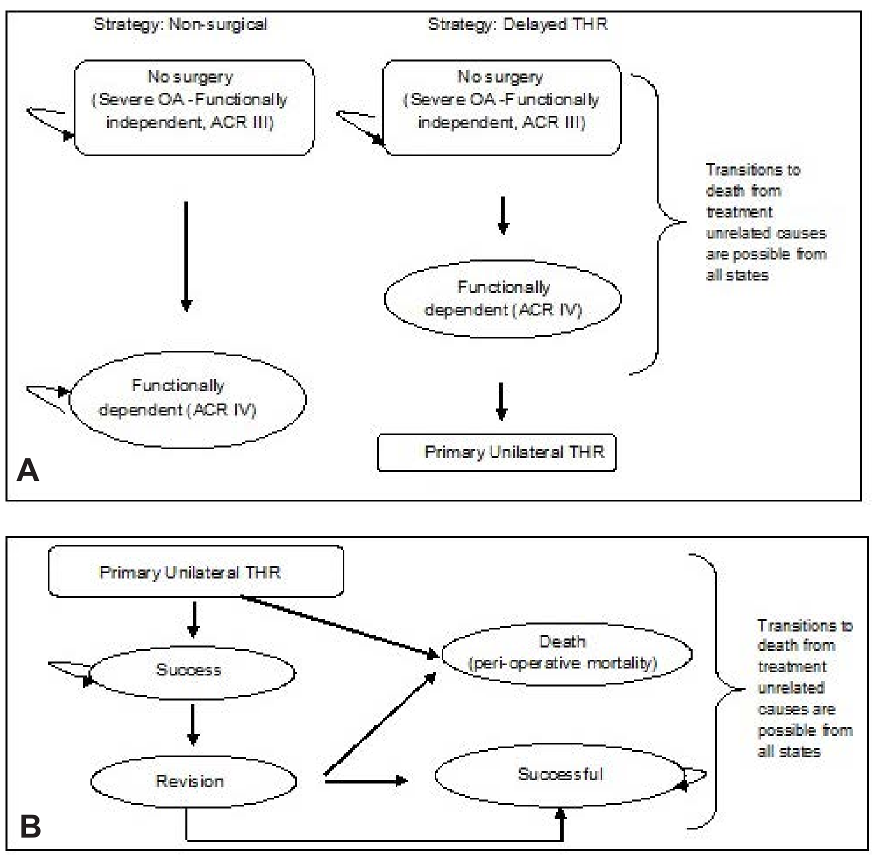


**Figure 1. Markov chain with annual cycles for non-surgical and delayed treatment (A); Markov model with annual cycles for total hip replacement (B).**

records on costs, and 12,990 records on health or HRQoL outcomes. A screening of titles and abstracts of these records (Appendix II) identified 75 articles for full text screening on health outcomes and 10 on cos Title and abstract and full text screening identified 17 studies (19 articles) on health-related outcomes and 8 studies on direct and indirect (productivity) costs or resource utilisation conducted in subjects living in Germany that met the criteria for inclusion in the review. A further 10 studies were identified from manual searches of reference lists from included studies and an updated search on cost studies that omitted the filter for *osteoarthritis/ arthritis*.

Studies not meeting the inclusion criteria for the sole reason of its country setting being other than Germany were used to populate model parameters for which data from German populations were not available.

## Model inputs

### *Effectiveness parameter: implant survival*

Five studies met the inclusion criteria and reported results adequately (Kaplan and Meier (K-M) implant survival curves). Because none of these studies provided nationally representative data, data on implant survival from the National Joint Registry (NJR) from England and Wales were used as the most relevant alternative source of mature data to German practice, despite possible differences in the types of cups used between the two countries.

Figure 2A compares the K-M implant survival curves from German studies in the under 65 age group with sex-specific NJR data on individuals aged 55-64, whilst Figure 2B presents the respective implant survival curves from German studies in the 65+ group with the sex-specific NJR curves in the 65-74 and 75+ groups. The NJR curves track the path of the most recent German study although there is an increasing divergence from the 6th year. This German study investigated the effect of 2nd generation Metal-on-Metal prostheses implanted as far back as 1994, whereas the NJR data includes all THR operations performed from 2003 onwards.[21-25]

Figure 3 illustrates the survival of implanted hips for primary THR by age (55-64 *vs.* 65-74) and gender, both overall and by fixation method. Fully cementless had lower survival than hybrid and cemented implants, suggesting that acetabular cups are driving their excess failure rate. The higher rate of failure in the younger group and among males is also evident in these data on all operations performed in England and Wales since 2003.[21] The position of the all THR curve relative to the curves for cemented and cementless operations reflects the predominant use of the former fixation method in the older group, and the primacy of the latter method among younger patients. A conference abstract recently published a 5-year implant survival rate of 96.11% for 336,759 primary hip replacements received by AOK members during 2005-2011.[26] In contrast, the corresponding rates for all THRs in England and Wales from the NJR data reviewed here were 97.52%, while the cemented rate was 98.46% and the uncemented 96.35%.[21] In our decision analysis we used the NJR as the best available source of implant survival data to describe the experience in Germany; the base case analysis adopted the ALL THRs data and the sensitivity analysis, for low and high revision rates, the cemented and cementless data depicted in Figure 3.

### *Effectiveness parameter: complications*

In-hospital deep vein thrombosis (DVT), pulmonary embolism (PE) and bleeding complication rates of 0.26%, 0.07% and 1.18% respectively were found in an observational study across 99 centres in Germany among 3,905 THR patients prophylactically treated with fondaparinux.[27] Approximately 4% were revision operations, and the majority of patients were aged 65 or older (no details were reported).

Data from the German national nosocomial infection surveillance system for 43,463 procedures from 48 hospitals revealed an event rate of severe surgical site infections of 0.77 per 100 elective THR surgeries.[28] Surgical site infection rates for primary THR in patients with arthrosis vary between German hospitals by volume.[29]

Likewise, among 149,000 AOK OA patients, the probability of 90-day DVT or PE was 0.96% (0.85% for top and 1.35% for bottom quintile volume).[30] The respective figures for mortality are 0.56% (0.48% and 0.93%) while, as expected in a sample like this, where 75% of patients were older than 63, femur fractures occurred at the high rate of 0.73 (0.58 and 1.09). These and other administrative data[31] suggest that health outcomes in routine German practice may differ from those in other countries such as Sweden and the UK.

We investigated the effects of excess mortality associated with walking disability in the functionally dependent state of the medical therapy arm in sensitivity analysis, where we applied a death hazard ratio of 1.27 [95% CI 1.10-1.47]), reported for walking-aid users with OA.[1,32-34] This figure is consistent with findings from English cohort[35] and other data[36] but contrary to some reports[37,38] (Appendix IV).

The values used to populate effectiveness parameters are presented in Table 1.[39-47] The preferred sources and values are used for the base case, whereas high and low values are used for sensitivity analyses. German sources were used for short-term complications of primary THR, whereas UK registry data were used for revision risk parameters. Since German data on short term complications of Revision THR were not available, these outcomes were imputed from the outcomes for primary THR based

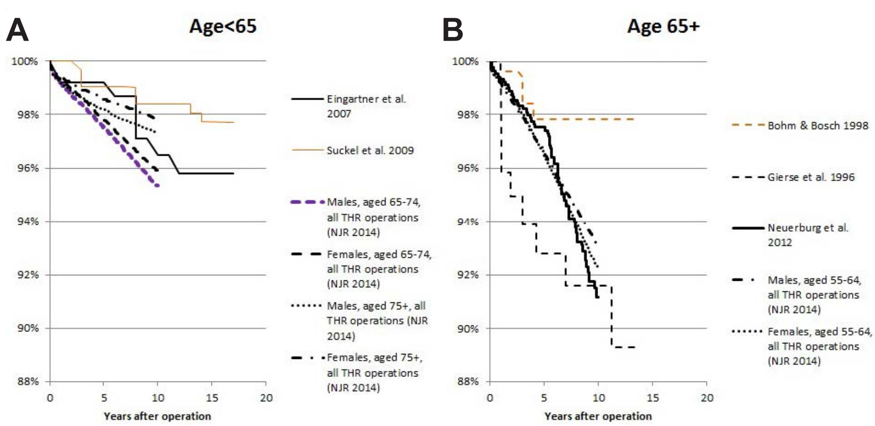


**Figure 2. Implant survival after primary total hip replacement in German experimental studies and registry data for England and Wales, by age group [age <65 (A) and age 65+ (B)]. Sample numbers (number of hips) are: Bohm and Bosch 1998:[22] at start n=264; 10 years n=9; 11 years (final) n=2. Gierse *et al.*, 1996:[23] at start n=106; at 14 years (final) n=73. Neuerburg *et al.*, 2012:[20] at start n= 1270; at 10 years (final); at 5 years n=1024; at 10 years (final) n=286. Eingartner *et al.*, 2007:[24] at start n=250; 10 years n=158; 13 years n=126; 14 years (final) n=30. Suckel *et al.*, 2009:[25] at start n=320; 17 years (final) n=97. As for National Joint Registry 2014,[21] at start, aged 55-64: Males n=63,806, Females n=77,260; aged 65-74: Males n=86,400, Females n=130,789; aged 75+ Males n=61,604, Females n=125,032.**

**Table 1. Effectiveness model parameters.**

| Parameter | | Value | | | Source |
|---|---|---|---|---|---|
| | | Base case | Low | High | |
| Primary THR | Peri-operative mortality: <75 years | 0.0056 | 0.0048 | 0.0093 | *90-day mortality*<br>Base case: Overall rate;[30]<br>Low: hospitals in top quantile by procedure volume per year;[30]<br>High: hospitals in bottom quantile by procedure volume per year[30] |
| | Peri-operative mortality: ≥75 years | 0.0151 | 0.0059 | 0.0167 | *90-day mortality*<br>Base case: Mid-point between rates for men and women aged≥80 in England and Wales (NJR);[40]<br>Low: Mid-point between rates for men and women aged 75-79 in England and Wales (NJR);[40]<br>High: Mid-point between upper 95% CI limit of rates for men and women aged ≥80 in England and Wales (NJR)[40] |
| Complications | Pulmonary embolous | 0.0096 | 0.0085 | 0.0135 | *90-day complications*<br>Base case: post-operative PE or DVT – OA sample;[30]<br>Low: Hospitals in top quintile volume of procedures performed per year;[30]<br>High: Hospitals in the bottom quintile volume of procedures performed per year[30] |
| | Wound infection | 0.0084 | 0.0077 | 0.0159 | Surgical site infections:<br>Base case: primary hip replacement for arthrosis in departments performing >100 procedures per year[29]<br>Low;[28]<br>High: Primary hip replacement for arthrosis in departments performing >50 and ≤100 surgeries per year[29] |
| | Bleeding | 0.0118 | 0.0096 | 0.0140 | Base case;[27]<br>Low and High: +/-20% |
| | Dislocation | 0.0239 | 0.0191 | 0.0287 | Base case: 90-day rate of dislocation;<br>Low and High:+/-20% |
| | Revision rates by sex and age (55-64, 65-74 and ≥75 - age groups) | Years 1-11 (%), 55-64 males: 0.88, 0.63, 0.60, 0.71, 0.64, 0.76, 0.73, 0.73, 0.78, 0.67, 0.81; females: 0.75, 0.58, 0.65, 0.80, 0.77, 0.85, 0.94, 0.91, 0.92, 0.81, 0.81. | Years 1-11 (%): 55-64 males: 0.55, 0.42, 0.42, 0.36, 0.37, 0.38, 0.38, 0.57, 0.58, 0.58, 0.58; females: 0.47, 0.35, 0.35, 0.40, 0.40, 0.39, 0.39, 0.55, 0.56, 0.56, 0.58. | Years 1-11 (%): 55-64 males: .92, 0.68, 0.68 0, 0.87, 0.88, 1.12, 1.13, 0.72, 0.73, ,0.73, 1.00; females: 0.88, 0.62, 0.62, 0.95, 0.96, 1.14, 1.16, 0.98, 0.99, 1.00, 1.00. | Base case: Annual revision hazards from cumulative incidence function (adjusted for competing death risk) for all primary hip replacement surgeries in England and Wales 2003-20012, digitally extracted from Figure 3.9 in NJR Annual Report 2014[21]<br>Low: Annual revision hazards from Kaplan-Meier survival rates of all cemented prostheses, Table 3.8[21] (years 2, 4, 6, 8, & 9 were calculated by interpolation of the reported K-M rates at adjacent years);<br>High: Annual revision hazards from Kaplan-Meier survival rates of all cementless prostheses, Table 3.8[21] (years 2, 6, 8, & 9 were c alculated from interpolation of the reported K-M rates at adjacent years);<br>After 10 years, the annual hazard rate was assumed to be constant at the highest 10th year hazard value of the two sex groups within each age group. Hazard rates for other groups are in Appendix III |
| Revision hip replacement | Peri-operative mortality: under 75 | 0.0060 | 0.0029 | 0.0091 | Base case, Low and High: calculated by the authors to equal the ratio of mortality risk in revisions to mortality risk in primary operations (2.23)[43] times the respective value for primary operation (presented at the top of this table) |
| | Peri-operative mortality: 75+ | 0.0237 | 0.0116 | 0.0359 | |
| Complications | Pulmonary embolous | 0.0153 | 0.0135 | 0.0215 | Base case, Low and High: Ratio of Revision to Primary 90-day THR PE risk,[41] *i.e.* 1.59, times PE risk for primary THR |
| | Wound infection | 0.0420 | 0.0385 | 0.0795 | Base case, Low and High: Ratio of Revision to Primary 90-day THR specific wound infection rate[41] *i.e.* 5, times primary wound infection rate |
| | Dislocation in men | 0.086 | 0.029 | 0.148 | Base case: 90-day rate of dislocation (non OA specific);[43]<br>female to male OR: 0.95;<br>Low: One third of base case;<br>High: 6-month cumulative dislocation incidence[44] |
| | Dislocation in women | 0.082 | 0.027 | 0.142 | |
| | Repeat Revision | 0.040 | 0.036 | 0.044 | Base case:[42,45] High/Low : +/- 10% |
| Medical therapy | Natural rate of progression to functional dependence (*i.e.*, ACR III to ACR IV) | 0.062 | 0.040 | 0.201 | Base case and High: based on authors' own estimates of transition after one year from primary data;[46]<br>Low: from geometric mean annual rate of transition of a 10-year cumulative incidence of functional dependence[39] |
| | All-cause mortality | Sex and age-specific | None | None | Base case: Period life tables for Germany 2009/2011[47] |
| | Relative excess mortality in ACR IV | 1 | 1 | 1.27 | Base case and Low: Assumption;<br>High: Adjusted hazard ratio of walking aid use[34] |

THR, total hip replacement; ACR, American College of Rheumatologists; OA, osteoarthritis.

on the incidence of complications of revisions relative to primary operations reported in studies of large US administrative data.[41]

### *Effectiveness parameter: quality of life (utilities)*

Due to the lack of data on utility values in German populations, values from UK, Finland and US studies were used. Table 2[48-64] presents the values used in the model. Pre-operative and 12-month post-operative values,[54] measured by the Euro-Qol 5-Dimension Questionnaire (EQ-5D),[55] were used to approximate the values of the states before disease progression in the non-surgical arm and the successful primary THR state in the model, respectively. The negative effects of delaying surgery on the utility of the successful THR state was derived from the difference in utility outcomes between patients with pre-operative HHS <40 and 70>HHS≥40.[3,56] The base case values for the need of Revision Surgery and Successful Revision states were populated from preoperative and postoperative revision hip replacement EQ-5D values.[57] Other utility values were used for sensitivity analysis.[58-63] Successul state utilities in the first year after THR and RHR were equal to 12-month post-operative values minus 3% to account for the patient's recovery from the operation.[64]

### *Healthcare costs parameterss*

Of the studies reporting THR costs in Germany,[52,65-71] the most representative source reported costs and outcomes of 154 470 AOK insured THR patients with OA.[71] The mean cost of primary surgeries in 2007-2009 was €7,221 (including first-year costs of inpatient treatment, €9,149). Revision surgery had a mean cost of €12,573. The additional costs of 90-day post-primary surgery complications and their rates were: dislocation, €3,697 in 2.39%; pulmonary embolism or thrombosis, €3,141 in 0.45%, femur fracture, €8,155 in 0.28%; and overall, €9106 in 3.84%.

The average cost of aseptic revision operations conducted between 2009 and 2012 at a single hospital was €4,380.[72] This estimate included the cost of surgery (63% of the total) and normal ward (27%), including physiotherapy, diagnostic tests, medications, intensive care unit, physician and nursing staff.

The mean cost of 49 total hip revisions for peri-prosthetic infection (26% occurred 1 year after implantation) in a Rostock hospital was calculated as €29,331. and the LOS was 52.7 days[73,74] (relative to the 2013 DRG reimbursement rate of €24,201, covering the hospital cost of two-stage septic revision,[73] our chosen estimate appears conservative).

We have found no data on medication, hospital or nursing home costs for severe OA patients treated by non-surgical means. We therefore imputed healthcare costs based on costs from Italy[3], adjusted for purchasing power cost differences between Italy and Germany.[75]

Table 3[71-86] presents the values used for cost parameters. Good quality information was found on costs of primary THR, healthcare in the first year post-primary THR, and

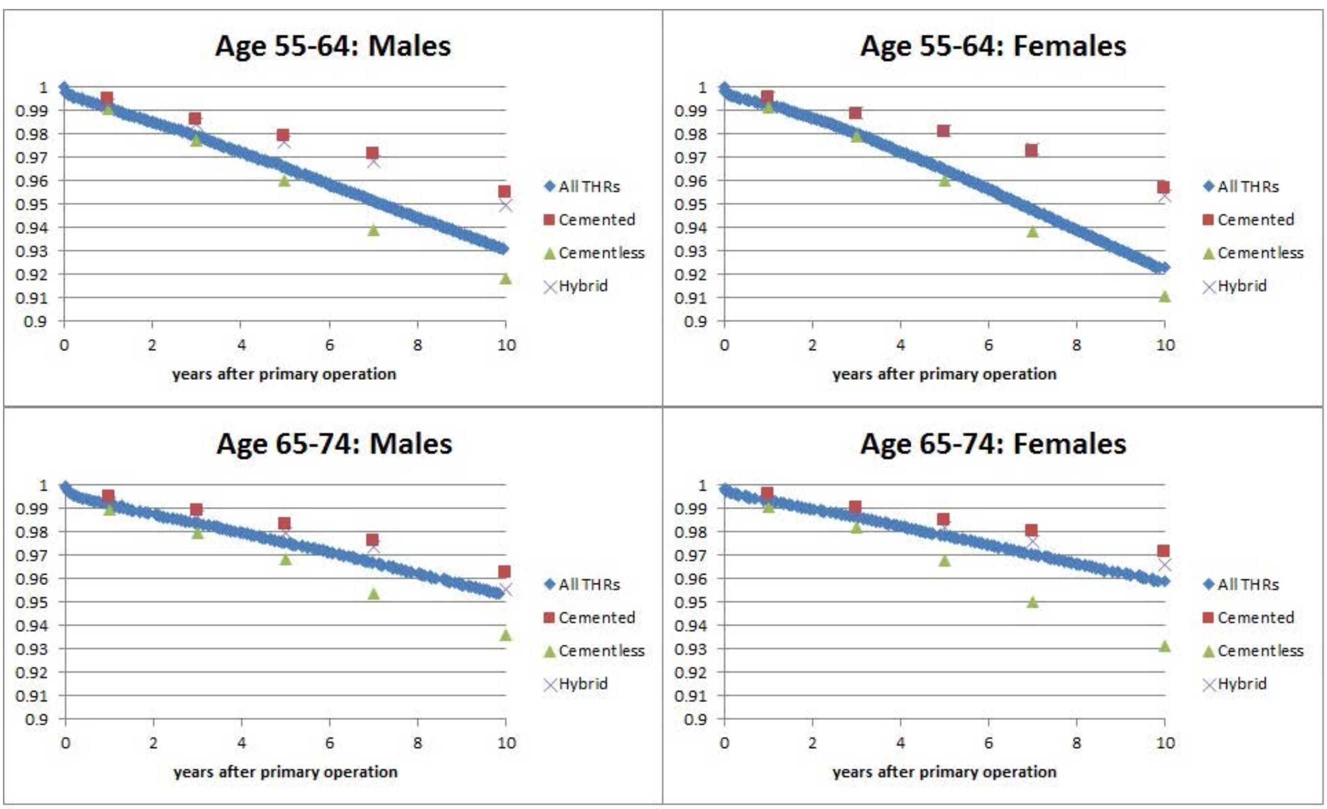


**Figure 3. Kaplan-Meier implant survival curves in National Joint Registry data for England and Wales. National Joint Registry Annual Report data, Table 3.8, and chart (digitally extracted data), Figure 3.9.[21] The curves for all total hip replacements are adjusted for competing risks of death and may not be entirely comparable to the curves for fixation modes. Sample numbers (number of hips) for cemented at start are: Age 55-64 male n=11,214; age 65-74 male n=31,396; age 55-64 female n=18,110; age 65-74 female n=56,158. Sample numbers (number of hips) for cementless at start are: Age 55-64 male n=32,236; age 65-74 male n=36,055; age 55-64 female n=39,357; age 65-74 female n=47,134. Numbers at risk after the start of follow up were not reported.**

revision THR. The only source of German data found for costs under the Medical arm[76] was of a lower reporting quality than the UK available source,[77] and was therefore used for sensitivity analysis, while UK resource use quantities[77] valued at German prices were used for the base case analysis. Due to limited data available on indirect costs[78,79] and nursing care costs,[80] these costs were not considered in the analysis.

## Model results

### *Base case results*

Table 4, presents base case results by gender for two hypothetical individuals, of age 55 and age 65 at the time of the decision whether to a) undergo timely THR, b) delay THR until physical condition deteriorates, and c) treat by medical therapy indefinitely. The costs are in Euros as at 2013 and the benefits in quality adjusted life years (QALYs), both discounted at 5% per year. Undiscounted costs and QALY figures are also presented in the table.

Undiscounted costs highlight the costs to a decision maker who values outcomes in the future as much as outcomes in the present. For such policy-maker, timely THR results in net healthcare cost savings for women aged 55 whereas it results in positive net costs for 55 year old men and for 65 year olds, relative to delayed THR and medical therapy. Undiscounted QALYs results reveal that a timely THR policy represents an average gain to an individual patient equivalent to between 3.15 extra years of life in full health for a 65 year old male, and 3.93 extra years of life in full health for a 55 year old female.

Timely THR is associated with ICERs below €2,000 in all instances, relative to Medical therapy or delayed THR. In all cases, undergoing THR whether timely or with delay results in additional (discounted) costs to the SHI system. Further, undergoing timely THR incurs additional costs relative to delayed THR. In a 55 year-old woman timely THR is expected to cost the SHI €4,782 more, on average, than if she was managed non-surgically; on the other hand, if she were turned away from surgery until her condition deteriorated to the extent of losing her functional independence (which at the base case rate of disease progression, 6% per year, implies a median delay of 11 years), her lifetime treatment would cost €1,363 more than non-surgical therapy. The resulting saving to the SHI from delaying THR, of €3,419, comes with a high cost to the patient since her benefits from delayed THR are only 2.86 (discounted) QALYs, instead of the 5.55 (discounted) QALYs with timely THR. Thus, the incremental cost per quality adjusted life year of timely THR is €1,270 per patient (see footnote ° of Table 4 for this figure).

**Table 2. Utility values.**

| State | | Base case | High Gain | Low Gain | Tool | Source |
|---|---|---|---|---|---|---|
| Medical therapy | Utility before Progression (ACR III) | 0.52 | 0.61 | 0.80 | EQ-5D<br>High Gain: TTO<br>Low: 15D | Base case: Mean pre-operative value of OA patients with no EQ-5D anxiety/depression. Value is for males; females: 0.47;[54]<br>High: Mean moderate OA pre-determined state assessed by elective THR patients[61]<br>Low: pre-operative mean from THR patients with 70>HHS≥40[56] |
| | Utility after Progression (ACR IV) | 0.28 | 0.39 | 0.77 | EQ-5D<br>High Gain: TTO<br>Low Gain: 15D | Base case: Mean pre-operative value of OA patients with moderate/severe EQ-5D anxiety depression. Value presented is for males; females: 0.25;[54]<br>High: Assumed equal to 66% of utility before progression value,[60] and mean severe OA pre-determined state assessed by elective THR patients;[59]<br>Low: pre-operative utility from THR patients with HHS<40[56] |
| Primary THR | Annual Successful primary THR | 0.83 | 0.96 | 0.86 | EQ-5D<br>High Gain: TTO<br>Low Gain: 15D | Base case: Mean post-operative value in patients with no pre-operative anxiety/depression on EQ-5D. Value is for males; the value for females is 0.80;[54]<br>High: Mean 12-month post-operative values;[61]<br>Low: Patients undergoing primary THR & 70>HHS≥40 in Finland (value is mean at 12 months for age 60-75; age 50-59, 0.90; age 75+, 0.81).[56] Includes 3% reduction in 1st post-operative year utility due to rehabilitation[64] |
| | Pre-operative revision hip replacement | 0.35 | 0.49 | 0.81 | EQ-5D<br>High Gain: TTO<br>Low Gain: 15D | Base case;[58]<br>High;[61]<br>Low: Mean 12 month post-operative values of Finish patients undergoing RHR[56] (presented value is for age 60-75; age 50-59, 0.86; age 75+, 0.80). Includes 3% reduction in first post-operative year to account for effect of rehabilitation[64] |
| | Successful RHR | 0.64 | 0.67 | 0.82 | | |
| Delayed THR | Pre-operative States ACR III/IV | Same as for THR | | | | |
| | Utility post-primary THR | 0.79 | 0.85 | 0.84 | Assumption<br>High: Assumption<br>Low: 15D | Base: Utility of annual successful THR minus the utility difference 12-month post-operatively between HHS<40 and HHS>=40 and <70[56] scaled up by the ratio of EQ-5D to 15D impact of hip/knee arthrosis.[65] Value is for males; females, 0.76;<br>High: Utility of annual successful THR minus the product of the regression to the mean coefficient from pre to 12 month post-operative utility scores times the difference in medical therapy utility before and after progression.[3]<br>Low: Mean at 12 months post-operatively,[56] patients undergoing primary THR with HHS<40 in Finland. Includes 3% reduction in 1st post-operative year due to effect of rehabilitation[64] |

THR, total hip replacement; ACR, American College of Rheumatologists; TTO, time trade-off technique; OA, osteoarthritis; 15D, 15 dimensional utility index; EQ-5D, EuroQol 5 dimension index; HHS, Harris hip score.

***Sensitivity analyses***

Table 5 presents the results of deterministic sensitivity analyses for the most influential model parameters. The utility gain with primary THR and the costs of primary THR (including implant costs) had the largest effects on the results, but ICERs remained below €9,000 in the most conservative scenarios. In comparison with the base case results, reproduced in the top row, the ICER for the delayed THR option relative to medical therapy is larger when THR extends survival, in the bottom row. The reason for this increase is that the severely affected patients who now die earlier under medical therapy consume a disproportionately large amount of healthcare resources. We performed a two-way sensitivity analysis to identify the minimum reduction in medical therapy costs at which life extension with THR resulted in a lower ICER

**Table 3. Unit costs (annual estimates in 2013 expressed in €).**

| Cost | Base case | Lower | Upper | Source |
|---|---|---|---|---|
| Primary THR- prosthesis and surgery | 7221 | 4582 | 11,944 | Base case;[71]<br>Lower: uncomplicated THR;[82]<br>Upper: mean +1.96 SD[82] |
| Cost of RHR | 12,573 | 4380 | 29,331 | Base case: Revision operations within the first year of primary surgery;[71]<br>Lower: Cost of aseptic loosening;[72]<br>Upper: Septic revision[73] |
| Medication use in *successful* state - 1st year after primary surgery or revision | 154 | 83 | 723 | Base case: As for 'medical therapy for severe OA', except for proportion of NSAID use: 0.478, where 0.08 at ≥90% of the year, and rest, 0.398, at (assumed, midpoint) 40% of the year;[77]<br>Lower/Upper: As Base case but with low/high NSAID prices |
| Monitoring and rehabilitation and inpatient hospital use in the year after THR | 3733 | 2986 | 4480 | Base case: In-patient hospitalization costs in the first year post-surgery (€1928)71 + 20% of total cost of surgery with rehabilitation (€1805);[66] *i.e.*, base case THR/0.80x0.20 (does not include planned outpatient follow-up visits; 92% of patients do not require follow of care in the first year);<br>Lower/upper: +/- 20% |
| Medication use in *successful* THR -2nd + years after primary | 117 | 63 | 550 | Base case: as in annual cost of medical therapy for severe OA except for proportion of NSAID use: 0.34, where 0.08 at 90% or more, and rest, 0.26 at assumed, midpoint) 40% of the year[77]<br>(costs applicable to states before revision);<br>Lower/Upper: As Base case but with high NSAID prices |
| Hospitalisations and physiotherapy-2nd year after surgery | 327 | 233 | 420 | Base case: unpublished data;[83] assumes equal to costs of Hospitalisations before progression times ratio of hospital costs ACR II to ACR III in RA.[8]4<br>Adjusted to German prices using relative price indices for health care (Fig. 6 in[85]);<br>Lower/Upper: 20% decrease/increase in hospital costs, 50% decrease/increase physiotherapy costs |
| Medical therapy for severe OA | 233 | 125 | 984 | Base case: NSAIDs consumption, Ibuprofen 2.4 mg/day, before THR, 90% and 40% of the year in 21% and 40% of patients, respectively;[77] 3 specialist visits. Includes cost of Gastro Protective Agents (GPA) and pre-administration tests;*<br>Lower: Nimesulide Ganules 30 bags of 100 MG (Sachet), 100 mg 2 x day;<br>Upper: Lower 95% CI of mean costs of medications, outpatient physician visits and non-physician services[80] reflated to 2013 prices° |
| Medical therapy for severe OA – with disease progression | 434 | 233 | 1308 | Base case: NSAIDs use 90% & 40% of the year by 50% of patients each –assumed;77 3 specialist visits. Includes cost of Gastro Protective Agents (GPA) and pre-administration tests;*<br>Lower: Nimesulide Ganules 30 bags of 100 MG (Sachet), 100 mg 2 x day;<br>Upper: mean costs of medications, outpatient physician visits and non-physician services;[80] reflated to 2013 prices° |
| Hospitalisations and physiotherapy for severe OA | 561 | 393 | 728 | Base case:[83] and unpublished data, imputed based on ratio of ACR III to ACRII hospital costs in RA.[84] Adjusted to German prices using relative price indices for health care (Fig. 6 in[85]);<br>Lower/Upper: 20% decrease/increase in hospital costs, 50% decrease/increase Physiotherapy costs |
| Hospitalisations and physiotherapy for severe OA – with disease progression | 832 | 563 | 1101 | Base case:[83] and unpublished data, imputed based on ratio of ACR IV to ACRII hospital costs in RA.84 Adjusted to German prices using relative price indices for health care (Fig. 6 in[85]);<br>Lower/Upper: 20% decrease/increase in hospital costs, 50% decrease/increase physiotherapy costs |
| Complications primary THR: DVT or PE | 3141 | 2513 | 3769 | Cost per (90-day post-operative) event;<br>Base: thrombosis or pulmonary embolism[71]<br>Lower/upper=+/-20% |

THR, total hip replacement; RHR, revision hip replacement; NSAID, non-steroidal anti-inflammatory drugs; OA, osteoarthritis; DVT, deep vein thrombosis; PE, pulmonary embolism; ACR, American College of Rheumatologists. *Includes visits to specialist in proportion to drug use. GPA prophylaxis and treatment costs were derived from NSAIDs costs and iatrogenic cost multiplier.83 Other drug (corticosteroids and analgesics) costs were derived by the same approach. °OA patients, not hip OA specific. Reflated using the Consumer Price of Health (sector 06) reported by Federal Statistical Office of Germany 2014; https://www.destatis.de/EN/FactsFigures/NationalEconomyEnvironment/Prices/Consumer PriceIndices/[86]

than the base case ICER; medical therapy costs (other than adverse events) would need to be 50% lower than under the base case in order for life extension with THR to translate in an improved ICER for the THR options relative to medical therapy. Notice that, in Table 5, the ICER of THR is relative to Delayed THR, as opposed to Medical Therapy, and is not affected by structural uncertainty about survival benefits, since no physical functioning dependence for a period longer than a year, and therefore increased death risk, is experienced under any of the two surgical options.

## Discussion

Our systematic search of the epidemiological and health services research literature sought to populate a cost-effectiveness model of end-stage OA treatment in Germany.

Implant revision rates from the national registry for England and Wales were used in the economic model, since no nationally representative data on the revision rates of THR in Germany were identified. Treatment practice in England and Wales was thought to be similar to that of Germany in terms of mode of fixation and implant selection and the national registry measured outcomes over a follow-up of ten years. Moreover, such data displayed implant survival curve profiles that were similar to the most recent German study in the relevant population.

The analysis was robust to a wide-range of variation in the preference valuation of generic health-related quality of life outcomes, and therefore uncertainty due to the lack of such data from German OA patients.

Limited information on healthcare costs for the medical therapy arm were found for Germany and were complemented with detailed data from the UK providing a range of plausible variation for sensitivity analysis. We could not find any study documenting productivity costs. Nevertheless recent evidence on productivity benefits for hip[87] and knee replacement,[88] suggests that THR has benefits beyond those realised in the healthcare system.

In our conservative analysis timely THR costs more to SHI than medical therapy and delayed THR. The expected benefit of having timely THR in terms of health related quality of life to patients is substantial, ranging from the equivalent of an additional 3.15 years of life in full health for a 65 year-old male person to 3.93 extra years of life in full health for a 55 year-old woman. This is remarkable given that (in the base case) THR produces no survival benefits (and a small excess peri-operative mortality risk) over medical therapy, so that all the QALY gain is due to the effects on quality of life. In sensitivity analyses we accounted for new evidence that walking disability is associated with reduced life expectancy, by accounting for an excess mortality risk after progression to a functionally dependent state under the medical therapy arm, so that in effect THR increases quantity, as well as quality, of life by avoiding disease progression.[34]

An observational study of THR relative to medical therapy in OA Medicare patients in the US, found that THR reduced mortality, heart failure and diabetes risk at 1 year and every two years until the 7-year end of study follow-up and increased cumulative OA and non-OA related healthcare non-prescription drug costs by US$6,366.[89] In our sensitivity analysis, survival benefits with THR improved its cost-effectiveness only if the counterfactual costs of medical therapy for severe OA under non-surgical therapy were less than €117 annually.

The only relevant existing study in Germany used long-term costs and benefit extrapolations from 6-month HRQoL outcomes and hospital resource utilisation by a group of 261 mostly OA patients of mean age 68 following primary or revision (n=10) THR.[90] It found that THR resulted in additional undiscounted QALYs of 5.95 relative to medical therapy and that more severe patients (*i.e.* low WOMAC scores) had larger QALY gains than patients with high WOMAC scores. In our study timely THR

**Table 4. Results: costs (expressed in €) and quality-adjusted life-years by sex and age at point of initial surgery decision (discounted at 5% annual rate, unless indicated otherwise).**

| Age group | Measure | THR | Delayed THR | Medical therapy | Difference THR- medical | Difference Delayed THR – medical |
|---|---|---|---|---|---|---|
| Females Age 65 | Costs undiscounted | 20,362 | 19,629 | 18,338 | 2,024 | 1,291 |
| | QALYs undiscounted | 14.58 | 11.04 | 7.37 | 7.20 | 3.67 |
| | Discounted Costs | 16,892 | 13,484 | 11,515 | 5,377 | 1,969 |
| | Discounted QALYs | 9.50 | 6.96 | 4.98 | 4.52 | 1.97 |
| | ICER | - | - | - | 1,190* | 999 |
| Females Age 55 | Costs undiscounted | 27,474 | 27,083 | 28,263 | -789 | -1,181 |
| | QALYs undiscounted | 20.68 | 16.74 | 10.26 | 10.42 | 6.49 |
| | Discounted Costs | 19,607 | 16,189 | 14,826 | 4,782 | 1,363 |
| | Discounted QALYs | 11.56 | 8.86 | 6.00 | 5.55 | 2.86 |
| | ICER | - | - | - | 861° | 476 |
| Males Age 65 | Costs undiscounted | 19,062 | 17,3714 | 15,538 | 3,524 | 1,832 |
| | QALYs undiscounted | 12.50 | 9.35 | 6.42 | 6.08 | 2.93 |
| | Discounted Costs | 16,298 | 12,347 | 10,193 | 6,105 | 2,153 |
| | Discounted QALYs | 8.49 | 6.16 | 4.51 | 3.98 | 1.65 |
| | ICER | - | - | - | 1,533# | 1,307 |
| Males Age 55 | Costs undiscounted | 24,964 | 24,168 | 24,264 | 700 | -96 |
| | QALYs undiscounted | 18.13 | 14.42 | 9.07 | 9.06 | 5.35 |
| | Discounted Costs | 18,684 | 15,095 | 13,450 | 5,234 | 1,644 |
| | Discounted QALYs | 10.65 | 8.06 | 5.56 | 5.09 | 2.49 |
| | ICER | - | - | - | 1,029§ | 659 |

THR, total hip replacement; QALY, quality-adjusted life-year; ICER, incremental cost-effectiveness ratio. *ICER *vs* Delayed THR=1,338; °ICER vs Delayed THR=1,270; #ICER vs Delayed THR=1,692; §ICER *vs* Delayed THR=1,385.

**Table 5. Sensitivity analysis: incremental cost-effectiveness ratio, additional € per quality-adjusted life-year gained.**

| Parameter | | Age 55 THR* | Age 55 Delayed THR° | Age 65 THR* | Age 65 Delayed THR° |
|---|---|---|---|---|---|
| Females | Base-case | 1,270 | 476 | 1,338 | 999 |
| | Conservative utilities (Low Gain) | 7,930 | 3,342 | 8,712 | 7,180 |
| | High costs of revision | 1,628 | 449 | 1,582 | 1,155 |
| | Low transition rate (20% reduction) | 1,474 | 529 | 1,585 | 1,075 |
| | High annual discount rate (7%) | 1,757 | 782 | 1,804 | 1,287 |
| | Low annual discount rate (3.5%) | 909 | 262 | 901 | 793 |
| | High hospital costs 1st year post-THR | 1,431 | 618 | 1,509 | 1,173 |
| | High primary THR costs (65% increase) | 2,090 | 1,356 | 2,298 | 2,155 |
| | High revision risks (in Table 2) | 1,379 | 554 | 1,542 | 1,115 |
| | Excess mortality - Medical therapy after progression to functional dependence | 1,270 | 600 | 1,338 | 1,156 |
| Males | Base-case | 1,385 | 659 | 1,692 | 1,307 |
| | Conservative utilities (Low Gain) | 8,760 | 4,652 | 11,096 | 9,444 |
| | High costs of revision | 1,885 | 941 | 1,946 | 1,484 |
| | Low transition rate (20% reduction) | 1,604 | 715 | 1,956 | 1,382 |
| | High annual discount rate (7%) | 1,868 | 969 | 2,161 | 1,605 |
| | Low annual discount rate (3.5%) | 1,026 | 441 | 1,341 | 1,092 |
| | High hospital costs 1st year post-THR | 1,555 | 812 | 1,889 | 1,500 |
| | High primary THR costs (65% increase) | 2,279 | 1,624 | 2,803 | 2,599 |
| | High revision rates | 1,515 | 729 | 1,836 | 1,391 |
| | Excess mortality - Medical therapy after progression to functional dependence | 1,385 | 811 | 1,692 | 1,479 |

THR, total hip replacement. *ICER *vs* Delayed THR unless Delayed THR is extended dominated (ED), in which case ratio is relative to Medical Therapy; °ICER relative to Medical Therapy, unless delayed THR is ED by early THR or dominates (has lower costs and more QALYs than) Medical therapy, respectively labelled ED and D.

for a 65 year-old had undiscounted QALY gains relative to medical therapy of 6.08 for men and 7.20 for women. In contrast, we found larger QALY gains for timely than among delayed therapy despite the more severe status of patients at the time of delayed THR and allowance in our analysis for larger pre to post-operative health gains of patients with more severe disease.[48] The reason for the different results between the two studies is that delayed THR arm in our study measured the expected QALY gains at the time the decision between timely, delayed or no surgery is made, whereas the results by disease severity reported by Vogl[90] are calculated at the time patients are operated and therefore, unlike our results, miss the loss in utility during any delay of treatment experienced by the more severe patients.

Vogl and colleagues found that THR was associated with positive undiscounted incremental costs of €7,730 relative to medical therapy, and reported higher costs among patients with more severe disease.[90] The undiscounted incremental costs of timely THR in a 65 year old in our analysis were instead €2024 in females, and €3,524 in males. The difference with our results is due to Vogl's assumption that the non-surgical costs in the THR arm were equal to those of the medical arm, whereas we accounted for higher non-surgical healthcare costs in the medical therapy arm than under timely THR, especially after disease progression. Further, our total costs of timely THR were higher than those of delayed THR. Unlike the analysis by Vogl and colleagues, in delayed THR a proportion of patients aged 65 years at the model baseline would die without undergoing surgery and therefore not incur the costs of primary THR. Moreover, discounting reduces the costs of the delayed arm, relative to timely THR, because primary surgery occurs later. Thus, at the 3.5% annual rate of discount used by Vogl for deriving their reported incremental cost per QALY with THR of €1,669,[90] timely THR has a respective figure of €901 in females and €1,341 in males aged 65.

## Conclusions

In conclusion timely THR in Germany is a cost-effective treatment policy under all plausible values of uncertain model parameters. Delayed THR represents an inefficient use of scarce healthcare resources.

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