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**The potential economic
role of regenerative
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of knee osteoarthritis**

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**The potential economic role of
regenerative therapy in the treatment
of knee osteoarthritis.**

**Cost-utility analysis for the
treatment of knee OA in three
European: Platelet-Rich-Plasma
dedicated kit *versus* Hyaluronic acid**

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Abstract

Background. Osteoarthritis (OA) is a chronic and degenerative pathology that affects joints in particular hands, knees, hip and lower back. The prevalence and incidence is in continuous increase for the advanced ageing of the population and the increasing presence of risk factors such as obesity. OA burden of disease implies high care costs and has an important social impact because it limits people's every day activities causing pain and mobility reduction.

Objectives. The aim of this work is to carry out an economic evaluation of the intra-articular (i.a.) use of the Platelet-Rich Plasma (PRP) therapy in the treatment for knee osteoarthritis. Recently the scientific literature has shown the effectiveness of this treatment. The comparator adopted is the Hyaluronic acid (HA) which represents the standard i.a. therapy. Both therapies can reduce pain, improving patient quality of life, and can help the patient to delay the joint surgery, that represents a high cost for the National Health System.

Methods. A cost-effectiveness analysis (CEA) were performed using a decision tree model. The effectiveness outcomes are reported in terms of Quality Adjusted Life Year (QALY). The costs are reported in Euro (€) currency evaluated in 2016. The adopted perspective is the Healthcare System and only direct cost have been included in the analyses. Deterministic and probabilistic sensibility analyses are reported in order to evaluate the robustness of the results and account for the different sources of uncertainty.

The analyses have been carried out for three European country: Germany, Italy and France

Results. The PRP therapy results more costly but also more effective than HA. Using a Willingness to pay thresholds of € 10,000/QALY, the PRP result the cost-effective therapy with respect to HA, for patient with moderate to severe knee OA.

Keywords: Platelet-Rich Plasma, Hyaluronic acid, cost-effectiveness analysis, Cost-Utility Analysis, Knee Osteoarthritis

Classification Numbers: C63, D61, I1

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1. Introduction

Osteoarthritis (OA) is a common chronic illness in older adults affecting joints in particular hands, knee and hip resulting in joint inflammation with associated pain, stiffness and loss of movement. Its onset is linked to several risk factors like age, gender, ethnicity, working activity and overweight [1-4].

The WHO Scientific Group on Rheumatic Diseases estimates that 10% of the world's population who are 60 years or older have significant clinical problems that can be attributed to OA [5]. OA is one of the main causes of musculoskeletal disorders (second only to back and neck pain), accounting for 17 million years lived with disability (YLDs) in 2010. Musculoskeletal diseases in 2010 were responsible for 169 million YLDs, inferior only to mental and behavioral disorders [6]. As shown in Global Health Observatory data repository musculoskeletal diseases are the 8th in the whole world and the 4th in western countries for disability adjusted life years (DALYs) [7]. OA results to be the 11th out of 291 pathologies for burden of disability (YLDs) and 38th per DALYs [8-9].

Prevalence in different countries

The prevalence differ from country to country. In France Knee OA prevalence was estimated in a range from 2.1% (population of 40-49 years old) to 10.1% (population of 70-75 years old) for men and 1.6 (40-49) and 14.9% (70-75) for women. The knee standardized prevalence was 4.7% for men and 6.6% for women, respectively [10]. In Italy Knee OA crude rate prevalence was estimated in a range 3.4 – 8.0% (5.4% on average with a population of 18-91) [66]].

The two studies above use symptomatic OA confirmed on radiographs. At our knowledge there are not recent published study on symptomatic OA prevalence in Germany. In a survey study on a total of 595,754 german patients (people aged 60 years or older) the prevalence of OA of the hip or knee were defined as having outpatient diagnoses (ICD: M16 or M17) in at least two quarters of 2014. The study found that 12.1% had OA of the knee [67].

Despite the studies above are not directly comparable the Global Burden of Disease Study 2010 (GBD) confirm a slightly higher prevalence in central Europe country. The study estimated the age-standardised prevalence of knee OA at

2.7% (2.3-3.1) for male and 4.5% (3.9 – 5.2) for female in Western Europe and 3.0% (2.4-3.7) and 5.0% (4.0-6.0) in central Europe countries [9]

Level of prevalence reflects on a burden for health systems.

According to data on Hospital discharges by diagnosis, provided by Eurostat, OA has an important and increasing impact on health care activity.

In 2015 France hospital discharges for OA (ICDI-10-M16 and 17) were around 209,000 (103,236 hip and 105,445 knee), that were the 2% of the discharges with an average hospital stay of 7.5 days.

These numbers are increasing steadily every year (see fig.1). In France hospital discharges for OA were around 156,000 (84,583 hip and 71,703 knee) in 2006 and 190,000 (97,654 hip and 92,902 knee) in 2012.

In Italy (2015) hospital discharges for OA were around 137,000 (63,766 hip and 73,283 knee), that were the 1.8% of the discharges with an average hospital stay of 9 days. In 2006 and 2012 hospital discharges for OA were respectively around 113,000 (54,282 hip and 59,036 knee) and 125,119 (57,953 hip and 67,166 knee) in 2012.

In 2015 in Germany hospital discharges for OA were around 566,000 (274,394 hip and 291,980 knee), that were the 2.7 % of the total number of discharges with an average hospital stay of 15 days. Unlike France and Italy the total number of hospital discharges after a steady increase decreased for some years and in 2015 was at the 2006 level. (see table 1 in appendix).

Figure 1. The increasing number of hospital discharges for OA – Source Eurostat

In western countries the rise of OA prevalence is leading to an increase in the number of total joint arthroplasty, which can be considered as the final stage of OA (knee and hip OA) [11-12].

In Italy and France the 90% of hospital discharge for knee OA are related to total knee replacement procedure, while in Germany only about the 50%. At the same time the TKR rate in Germany are higher than in the other two countries (see Table 2 Appendix)

A work on Total Knee Replacement (TKR) incidence, showed the annual growth varies by country, from the 17% and 14% of Portugal and Switzerland to the 7% of Germany. In France the compound annual growth in the incidence of TKA was estimated around 5.3% [13].

Eurostat data show the increasing trends for total joint replacement (TJR) (see table 2 in Appendix)

The increasing incidence of total joint arthroplasty reflects the rise of OA prevalence. OA disease has a significant impact on patient quality of life causing

pain, stiffness and decreased joint functionality, leading to social life limitations and loss of work productivity.

The burden of OA is correlated to a high economic impact in terms of both direct health-related costs and indirect costs. The heterogeneity of cost-of-illness studies do not allow to have a clear amount of cost related to OA. In western countries, where the prevalence is higher, the total costs relating to treatment for OA are estimated at between 1% and 2.5% of Gross Domestic Product (GDP)¹⁴. A recent systematic review concludes that the social cost of osteoarthritis could be between 0.25% and 0.50% of a country's GDP¹⁵. A review of 32 cost-of-illness studies states that the weighted average annual costs per patient living with knee and hip OA is € 11100, € 9500 and € 4400 for total, direct and indirect costs, respectively [16].

OA costs may vary considerably between countries and population.

A Canadian study estimated direct health related costs in Canadian dollars (CAD) \$2233 per patient per year [17], while a Dutch study found indirect costs due to loss of productivity in € 722 (with median € 217) per patient per month [18]. In Italy annual total costs per patient have been estimated in € 3000 (€ 1300 as direct health-related costs and € 1700 as indirect costs adjusted in 2013) [19].

In France, the study by Le Pen et al. estimated that healthcare costs (doctor visits, medicines, and hospitalizations) for patients with osteoarthritis account for around 1.7% of France's total healthcare expenditure in 2002 [20].

Bertin et al. provide a health economic update of the patient costs associated with hip or knee OA treated in the community and in medical, surgical and obstetric care (MSO) and post-acute care and rehabilitation (PAC) hospitals in France in 2010. The annual costs per community patient were € 715 and € 764 for hip and knee OA, respectively, including a cost to the healthcare system of € 425 and € 454, that is, an estimated € 3.5 billion (€ 2 billion to the healthcare system) for 4.6 million patients. Hospitalization engendered annual costs of € 9,797 per patient with hip OA and € 11,644 per patient with knee OA, that is, a total cost of € 1.955 billion for patients hospitalized for hip or knee OA in 2010 [21].

The main direct health-related cost driver is the total joint arthroplasty [22]. The steady increasing, year after year, of surgery incidence lead costs to grow [22-23] for the foreseeable future [11-12].

Epidemiologic and economic trends can put under pressure the National Healthcare Systems. There is the need to find out how to manage and restrain the growth of these costs or to find alternative solutions to reduce them. A possible strategy to adopt consists in slowing down the progression of the pathology in order to delay (or to avoid) the surgery [24-27]. Hyaluronic acid (HA) and platelet-rich-plasma (PRP) are two intra-articular (IA) infiltration therapies used between the pharmacological and the surgical phase, in order to delay or to avoid the surgical intervention. In a stated preference analysis on willingness to pay for OA treatments, viscosupplement knee injections were considered the therapy with the highest levels of satisfaction by the largest proportion of patients with respect to conservative treatments. [28].

The objective of the present study is to assess the cost-effectiveness of the intra-articular PRP therapy with respect to HA, in three European countries (France, Italy and Germany), for patients with mild-moderate to severe knee pain due to OA and who failed to respond to conventional therapy, usually represented by corticosteroids.

Intra-articular Therapies: Platelet-Rich-Plasma and Hyaluronic Acid

Hyaluronic acid (HA) is an important visco-elastic component of the synovial fluid present inside the joints with lubricant and cushioning properties. When a patient is affected by OA, the concentration and molecular weight of HA gets lower losing its properties. From the clinical practice it is shown that an infiltration of HA in the joint can restore temporarily the patient's health, giving him relief. Several clinical studies show the HA efficacy in knee OA treatment [29-32], moreover HA, compared to corticosteroids infiltrations, has a longer lasting effect [27,33]. Considering direct cost and costs associated to potential side effects, it has been shown the cost-effectiveness of HA compared to oral NSAIDs (non-steroidal anti-inflammatory drugs), physical therapy and assistive device³⁴. HA has been used for several years and it is considered a standard intra-articular therapy in the treatment of knee OA.

PRP is a non-transfusion use blood component, used to treat pathologies with topical use or IA injections. It is collected from the patient's blood and used on the same patient, for this reason it is considered as a safe practice [35-36]. The PRP treatment efficacy is shown in several studies, in particular in the first year of treatment [36-41].

PRP is produced by the centrifugation of whole blood yielding a concentration of platelets above baseline levels. The benefits can be due to the platelet-derived growth factors introduced into the knee. These growth factors act in chondrocytes to promote cartilage matrix synthesis, increase cell growth and migration, and facilitate protein transcription. The release of platelet-derived factors directly at the site of cartilage disease including OA may stimulate the natural healing cascade and the regeneration of tissue and further mediate the anti inflammatory response [42].

In literature are reported several studies that compare HA and PRP effectiveness. Intra-articular PRP injections probably are more efficacious in the treatment of knee OA in terms of pain relief and self-reported function improvement at 3, 6 and 12 months [36,43-50]. The results of several meta-analyses confirm the major effectiveness of PRP [51-58].

The method to produce PRP needs a medical device and a longer time consuming process, leading the therapy to be more costly than the comparator(HA). The medical device taken as reference for this work is the Regen kit BCT-1©, manufactured by Regenlab (CH). The preparation of PRP starts taking a blood sample from a patient's vein (8 ml). The blood is put in the BCT-1 kit tube that contains an anticoagulant to prevent the activation of the platelets and a cell selector gel that permits separation of red cells from other blood components. The BCT-1 tube is then submitted to a centrifugation at a speed of 1500 g-force (3400 RPM), which enables to obtain three components: red blood cells trapped under the gel, Platelet-Poor-Plasma (PPP) and PRP settled on the surface of the gel. By gently inverting the BCT-1 tube several times, it is possible to suspend cellular deposit in the supernatant and obtain PRP (about 4 ml). Then PRP is ready for use, collected by a sterile syringe it is injected into the patient's joint [39,59].

2. Materials and methods

2.1 Study design

A decision tree model that evaluates the choice between PRP and HA for OA knee disease has been developed, considering costs and clinical benefits of both therapies. In this model the root node of the tree represents the choice between the two therapies (PRP and HA) for the knee OA treatment. From this choice depart several paths and treatments that the patient could be submitted at. For both the therapies the first node splits the path in two, according to the positive or negative response to the therapy. The development of the tree is represented in Figure 1. The decision tree considers a time horizon of one-year because there are not clinical studies with a longer follow up.

The results are reported both in terms of Incremental Cost-Effectiveness Ratio (ICER). The incremental cost-effectiveness ratio (ICER) is a statistic used to summarize the cost-effectiveness of a health care intervention. It is defined by the difference in cost between two possible interventions, divided by the difference in their effect. It represents the average incremental cost associated with 1 additional unit of the measure of effect.

The outcomes express the additional costs implied by the adoption of PRP to gain an additional life year in perfect health status.

Fig. 1 Cost-effectiveness model of PRP vs HA

2.2 Parameters of the model

Clinical data sources and derivation of utility values

The main measure of effectiveness used is the Western Ontario McMaster Osteoarthritis Index (WOMAC) total score. The clinical studies on the therapies report effectiveness in terms of WOMAC scale (that represents an illness specific measure of outcome widely utilized for lower extremity symptoms and function. Patients have to answer to a questionnaire assessing their status for three disease related domains: pain, stiffness and functionality.

The scores are summed for items in each subscale, with possible ranges as follows: pain=0-20, stiffness=0-8, physical function=0-68.

Total scores can range from 0 to 96, with higher scores indicating increased pain and stiffness, and decreased physical function. We rescaled the scores so that a higher number indicated a better outcome.

WOMAC as every Illness specific scales is very sensitive to changes and accurate to evaluate improvements in patients' conditions. On the other hand they are not comparable with standard willingness to pay threshold used to determine the cost-effectiveness of a therapy and the results are not generalizable outside the specific disease. Generic preference-based measures have been developed to allow comparisons. The most commonly used include the EuroQol (EQ)-5D5L, the Short Form 6D (SF-6D) and the Health Utilities Index (HUI). To see how they are build see [61]. In this work we used the QALYs (quality adjusted life years) to measure effectiveness. It has values between 0 (dead) and 1 (perfect health), negative value are possible when the health status is considered worse than death. Illness specific scales can be transformed in QALYs using mapping techniques. In this work WOMAC scores were transformed in QALYs using the conversion procedure of Wailoo [62] which it has been showed to be the best performer mapping algorithm in literature [63] and uses a mixture model derived from a study where patients states are both expressed in terms of WOMAC and EQ-5D5L. The model predict HRQoL using demographic variable, WOMAC pain, stiffness and function subscales.

We chose to use two studies to extrapolate data on effectiveness [47,49] because i) both studies have an improvement in WOMAC scores that is consistent with the metanalyses (a range of 15-25% WOMAC scores improvement), ii) the

information useful to map WOMAC in QALYs iii) this studies represent two different level of symptomatic knee as assessed through the WOMAC scale (one has lower WOMAC score [47], that is milder knee OA and the other higher WOMAC score [49]). iii) in addition, despite the mapping algorithm chosen perform well, it has been showed as at different level of WOMAC scores the algorithms can report biased results. We limit the bias using two different level of WOMAC scores.

In regard to the probability to respond at the two therapies, several studies show a response rate that ranges between 70% and 90% for both treatments [29-30,40-41]. For the base case scenario we chose to set the probability of clinical effectiveness at 80% for both of the therapies. This parameter varies in sensitivity analysis.

Resources use and costs

The costs for the two i.a.therapies are shown in table 1. PRP is more costly. Its higher cost is due by the cost of the product/device used and by cost of the process with the medical professionals involved.

PRP has a longer process. The 'production' of PRP implies several preparation steps (as previously described) and need longer times for elaboration, 11 minutes for PRP against 2 minutes for HA. The model take into account These differences in delivery. The duration of the PRP preparation process have been collected by interview to clinicians from different health structure in different countries. (Local Health Authorities (Unità Locale Socio Sanitaria, ULSS) of transfusional centres in Veneto region, Italy, Rhumatologie, Hopital de Meulan-Les Mureaux, France, and Klinik für Orthopädie und Unfallchirurgie UKSH Lübeck, University, Germany) (table 1). On the other hand HA treatment needs the IA injection time, while the PRP treatment needs two minutes for the plasma withdrawal from the patient, around 7 minutes for the centrifugation and the other operations previously cited and finally 2 minutes for the injection that are in common for both therapies. Finally, the additional time to produce PRP with respect to HA is 9 minutes.

We include in the model the extra time due to produce PRP and the cost for the additional time needed. Therefore we modeled the higher resource use for the PRP therapy process.

The cost of the medical device refer to the market price of the Regenkit BCT-1.

In regard to HA costs, the market price of Hyalgan product has been used. This product is one of the most used with a relative cheap price. Moreover it is the product used in one of the two clinic studies taken as reference to derive utility scores [47]. In addition, given the possible fluctuation of product market prices and also the use of different products a sensitive analyses has been carried out on this parameter.

Hospital doctor cost per minute was obtained through interview to clinicians from different health structure in different countries. (Local Health Authorities (Unità Locale Socio Sanitaria, ULSS) of transfusional centres in Veneto region, Italy, Rhumatologie, Hopital de Meulan-Les Mureaux, France, and Klinik für Orthopädie und Unfallchirurgie UKSH Lübeck, University, Germany) 60 (see table 1)

General costs were not inserted in the analysis because there is no significant difference and they do not change the results. The number of injections included

for a PRP therapeutic cycle is 3, as reported in the most recent meta-analysis [51-54]

2.3 Cost-effectiveness and Willingness to pay threshold

In conclusion in this work we report the results in terms of QALY. The cost effectiveness is assessed using the ICER.

The ICER reports the incremental cost for a gain of one QALY for the new therapy, that is the incremental cost for a gain of a year of life with perfect health thanks to the new health technology. In cost-effectiveness analysis the ICER value is compared with a WTP threshold.

In this study we refer to two standard levels that are 30,000 and a conservative 10,000€/QALY WTP, but at the same time we reported sensitivity analysis on different WTP thresholds. In fact we showed the cost effectiveness acceptability curves for every scenarios. In this way the decision makers can have a complete view.

2.4 Sensitivity analysis

Deterministic and probabilistic sensitivity analysis have been conducted to assess the impact of the uncertainty of the parameters used in the model on the results. Deterministic and probabilistic sensitivity analyses are useful to face different uncertainty as: i) model uncertainty, every model it is a simplification of the reality, ii) parameter uncertainty, in the estimation of costs and effectiveness iii) heterogeneity, that is the individual variability between patients. Therefore the sensitivity analyses have been run for the most important parameters of the model (table 1)

Deterministic sensitivity analysis (DSA) has been run for every min-max scenario of any parameters. In detail one way DSA have been run for every parameter where a min and max scenario is reported. Probabilistic sensitivity analysis (PSA) was performed through a Montecarlo simulation, performing 10,000 cases, to assess the uncertainty around the ICER/ICER and the probability of the PRP therapy to be cost-effective at different willingness to pay thresholds. At each model input parameter was assigned a probability distribution (table 1), that

describe the different value the parameter can have with different probabilities. The effectiveness has been modelled with uniform distributions to model the potential uncertainty around the differential effectiveness of the two therapies. The costs were represented as Gamma distributions as recommended in literature⁶⁴. The medical doctor per minute cost was described using a log-normal distribution because we wanted to introduce the case of a higher tariff for not hospital doctor. For the parameters cited in literature where it was not estimated standard error, it was assumed a general standard error of 25% of the mean value [65].

Results

We report here the report for the Germany and the synthetic results for all the three countries.

QALY scenario 1

In the base case scenario none of the therapies dominates the other, but PRP results the cost-effective therapy. The average cost per QALY is respectively around € 335 for HA and € 602 for PRP. The incremental effectiveness of PRP is 0.0472 QALY with an incremental cost of 200 €. The ICER of PRP introduction is €4,237/ QALY (Figure 2) that is under the € 10,000 WTP threshold used in the cost-utility analysis.

The analysis shows that the ICER calculated is sensitive according to the HA and PRP effectiveness, and the HA and PRP therapeutic cycle cost. In the table 3 the variations in the results that would be caused by extreme values of cost and effectiveness parameters analysis are showed. However, no variation of the parameters change the base case scenario result, that looks quite robust (from 1,659 to 7,575 €/QALY). The PRP does not become a cost saving therapy (dominant), even in the best case scenario, but in every scenarios it is the cost effective therapy.

Fig. 2: Cost-effectiveness plane (ICER) PRP vs HA

Tab. 2 Results of one-way sensitivity analysis, Costs and effectiveness parameters (Germany)

Parameters		Therapy	Cost (€)	Incremental Cost	Effectiveness (QALYs)	Incremental effectiveness	ICER (€/QALY)
PRP Effectiveness	Min	PRP	419	200	0.686	0.033	6,097
		HA	219		0.653		
	Max	PRP	419	200	0.729	0.076	2,631
		HA	219		0.653		
HA Effectiveness	Min	PRP	419	200	0.700	0.066	3,049
		HA	219		0.634		
	Max	PRP	419	200	0.700	0.026	7,575
		HA	219		0.674		
PRP RegenKit BCT-1 Cost	Min	PRP	337	118	0.700	0.047	2,500
		HA	219		0.653		
	Max	PRP	508	289	0.700	0.047	6,122
		HA	219		0.653		
HA Hyalgan cost	Min	PRP	419	228	0.700	0.047	4,830
		HA	191		0.653		
	Max	PRP	419	180	0.700	0.047	3,813
		HA	239		0.653		

The probabilistic sensitivity analysis was performed through a Monte Carlo simulation considering 10,000 scenarios (or cases). All the parameters and variables of the model vary according to the assigned distribution. Establishing a WTP of €10,000 per QALY, the PRP is cost-effective in the 72% of the scenarios (figure 4), while considering a WTP of €30,000 the PRP is cost-effective in 80% of the iterations. In figure 5 is reported the corresponding acceptability curve with the WTP threshold. For every WTP thresholds is indicated the percentage of cases in favor of PRP or HA, where the % of iterations cost-effective are derived from a probabilistic sensitivity analysis performed through the Monte Carlo simulation.

Fig. 4 Cost-effectiveness plane of joint distribution of incremental cost and effectiveness for PRP. In the plane are reported 10,000 different cases according to the joint distribution of the variables. The diagonal line represents the WTP threshold of € 10,000/QALYs.

Fig. 5 Cost-effectiveness acceptability curve of PRP vs HA under various WTP thresholds.

QALY scenario 2

The base case of the scenario with more severe WOMAC scores confirms that none of these therapies dominates the other, but PRP results the cost-effective therapy. The average cost per QALY is respectively around € 1,559 for HA and € 1369 for PRP. The incremental effectiveness of PRP is 0.166 QALY with an incremental cost of 200 €. The ICER of PRP introduction is €1,207/ QALY (Figure 6).

The results confirm the results of the scenario 1. The ICER is even lower for the base case scenario of severe symptoms

The most sensitive parameter is the effectiveness of the two therapies. In this case the PRP have a greater effectiveness (in fact in the base case the ICER is lower) but also have a greater variability because the clinic study used⁴⁹ report a higher standard deviation. However, no sensitivity analysis of the parameters changes the base case scenario result, that looks quite robust (considering the best-worst of the one way sensitivity analysis the ICER range from around 600 to 8,500 €/QALY). The PRP does not become a cost saving therapy (dominant), even in the best case scenario, but in every scenarios it is the cost effective therapy (according to a € 10,000 WTP).

The results confirm the results of the scenario 1. The most sensitive parameter is the effectiveness of the two therapies. In this case the PRP have a greater effectiveness (in fact in the base case the ICER is lower) but also have a greater variability because the clinic study used⁴⁹ report a higher standard deviation. However, no sensitivity analysis of the parameters changes the base case scenario result, that looks quite robust (considering the best-worst of the one way sensitivity analysis the ICER range from around 600 to 8,500 €/QALY). The PRP does not become a cost saving therapy (dominant), even in the best case scenario, but in every scenarios it is the cost effective therapy (according to a € 10,000 WTP).

The probabilistic sensitivity analysis was performed through a Monte Carlo simulation considering 10,000 scenarios. All the parameters and variables of the model vary according to the assigned distribution. Establishing a WTP of €10,000 per QALY, the PRP is cost-effective in the 99% of the scenarios (figure 8), while considering a WTP of €30,000 the PRP is cost-effective in 100% of the iterations

. In figure 9 is reported the corresponding acceptability curve with the WTP threshold. For every WTP thresholds is indicated the percentage of cases in favor of PRP or HA.

Country Comparison

The results reported for the Germany are quite similar to analyses made for France and Italy.

In table are showed the synthetic results for the three country.

Summary		ICER €/qaly			PSA - Probabilistic sensitivity analyses	
Country	OA	Base case scenario	Min	Max	% CE cases WTP 10,000	% CE cases WTP 30,000
Italy	Severe	606	333	4400	99	99
	Milder	2127	1300	3439	77	80
France	Severe	761	500	5500	99	99
	Milder	2675	1659	4847	76	80
Germany	Severe	1207	644	8500	99	99
	Milder	4237	2500	7575	72	80

CE cases= the percentage of cases cost effective in montecarlo simulation

4. Discussion

PRP and HA are therapies able to give relief to patients affected by OA, and to potentially reduce, or at least delay, the surgical intervention to replace the joint

[29-34,37-50]. Several studies show that PRP is more effective than HA36,43-58. PRP is a promising therapy for knee OA patients who do not respond to conservative treatments. The relative uncertainty around the major effectiveness of PRP with respect to HA has been included in the model using the uniform distribution in the probabilistic sensitivity analyses. No economic analysis of PRP in the treatment of knee OA has previously been reported. Therefore, the authors consider it significant to carry out this study, as first economic evaluation to establish the economic value of this therapy for knee OA, in addition to evidence of safety and effectiveness. Results obtained from the model show that for patient with a mild to severe knee OA, considering a time horizon of 1 year in the French system context, PRP therapy is cost-effective with respect to HA. Even if the PRP production process implies additional costs, this therapy can be considered cost-effective. Each country has an official or unofficial cost-effectiveness threshold for evaluating the cost-effectiveness of a therapy. In this study we refer to a conservative 10,000€/QALY WTP valid for every country studied and at the same time we developed sensitivity analyses on the WTP thresholds. In fact we showed the cost effectiveness acceptability curves for every scenarios. In this way the decision makers can have a complete view.

However even considering a conservative WTP threshold (€ 10,000.00/QALY) PRP is cost-effective. It is worth noting that cost computations include only direct health-related costs. The study did not consider, for example, cost due to loss of productivity and social life activities. Given the relative major effectiveness of PRP, including social costs could favor even more PRP therapy.

These results can be considered robust and accurate although they come from a decision analytic model that is a simulation and a simplification of real world. In this regard some limitations can be identified in the model. First the reported cost-effectiveness ratio may be influenced in relation with the method used to convert WOMAC scores in QALYs and for this reason we mapped the QALY from two different studies. Secondly a chronic disease should be evaluated in a longer period of time. The lack of clinical evidences on longer-term follow up does not allow to use a decisional model more accurate to define a model for the chronic illness on a long term. Yet it is to be further studied, a long term model able to take into account the surgical intervention in the analysis. The economic impact of TKR in NHS is an important variable to take into account for the economic

evaluation for the introduction of new therapies for knee OA. A more effective therapy can delay of some years TKR and this delay could lead to reduce the total OA economic impact on Healthcare Systems. Yet the definition of the structure of this study will be useful to extent the evaluation when more reliable data will be collected.

5. Conclusion

In conclusion, despite the limits explained above, it is possible to state that the IA PRP-based therapy is cost-effective with regard to the IA HA considering a one year horizon. Future research should evaluates PRP effectiveness for a longer period, in particular with reference to the delay of TKR. The major effectiveness of PRP, in addition to quality-of-life improvement, could delay TKR and therefore reduce also eventual prosthesis revision reducing the total costs of the knee OA and the economic burden on Healthcare Systems.

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Appendix

Table 1 Number of hospital discharges for OA – France. Source Eurostat.

France				
	Hip OA	Knee OA	rate per 100,000 (knee)	Total Hospital discharges fo OA
2006	84,583	71,703	115	156,286
2007	86,562	76,127	122	162,689

2008	88,656	78,304	126	166,960
2009	90,735	81,288	130	172,023
2010	92,759	84,22	135	176,979
2011	96,831	89,354	143	186,185
2012	97,654	92,902	149	190,556
2013	99,791	96,619	155	196,410
2014	103,236	103,334	166	206,570
2015	103,611	105,447	169	209,058
Italy				
	Hip OA	Knee OA	rate per 100,000 (knee)	Total Hospital discharges fo OA
2006	54,282	59,036	98	113,318
2007	56,791	64,810	108	121,601
2008	57,024	66,430	111	123,454
2009	58,188	67,458	112	125,646
2010	55,895	65,770	110	121,665
2011	56,620	65,549	109	122,169
2012	57,953	67,166	112	125,119
2013	59,350	68,398	114	127,748
2014	61,427	70,904	118	132,331
2015	63,766	73,283	122	137,049
Germany				
	Hip OA	Knee OA	rate per 100,000 (knee)	Total Hospital discharges fo OA
2006	257,585	291,004	353	548,589
2007	265,998	307,357	373	573,355
2008	270,064	315,106	383	585,170
2009	271,402	318,023	386	589,425
2010	270,601	315,478	383	586,079
2011	271,145	309,930	376	581,075
2012	267,375	304,810	370	572,185
2013	258,78	283,019	344	541,799
2014	271,656	288,554	350	560,210
2015	274,394	291,980	355	566,374

Table 2 Total join Replacement over 100,000 individuals (Source Eurostat)

Total Joint Replacement rate per 100,000 (inhabitants)						
	TKR (Knee)			THR (Hip)		
Year	Germany	France	Italy	Germany	France	Italy
2006	173	89	82	173	206	137
2007	188	98	90	188	209	150
2008	199	100	94	199	213	157
2009	205	102	95	205	217	158
2010	205	99	99	205	220	164
2011	205	99	100	205	225	166
2012	201	101	103	201	229	171
2013	186	103	105	186	234	175
2014	194	107	109	194	238	181
2015	204	110	113	204	242	188