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RESEARCH ARTICLE

Early health economic modelling of single-stage cartilage repair. Guiding implementation of technologies in regenerative medicine

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Abstract

Both the complexity of clinically applied tissue engineering techniques for articular cartilage repair – such as autologous chondrocyte implantation (ACI) – plus increasing healthcare costs, and market competition, are forcing a shift in focus from two-stage to single-stage interventions that are more cost-effective. Early health economic models are expected to provide essential insight in the parameters driving the cost-effectiveness of new interventions before they are introduced into clinical practice. The present study estimated the likely incremental cost-effectiveness ratio (ICER) of a new investigator-driven single-stage procedure (IMPACT) compared with both microfracture and ACI, and identified those parameters that affect the cost-effectiveness. A decision tree with clinical health states was constructed. The ICER was calculated by dividing the incremental societal costs by the incremental Quality Adjusted Life Years (QALYs). Costs were determined from a societal perspective. A headroom analysis was performed to determine the maximum price of IMPACT compared with both ACI and microfracture, assuming a societal willingness to pay (WTP) of €30 000/QALY. One-way sensitivity analysis was performed to identify those parameters that drive the cost-effectiveness. The societal costs of IMPACT, ACI and microfracture were found to be €11 797, €29 741 and €6081, respectively. An 8% increase in all utilities after IMPACT changes the ICER of IMPACT vs. microfracture from €147 513/QALY to €28 588/QALY. Compared with ACI, IMPACT is less costly, which is largely attributable to the cell expansion procedure that has been rendered redundant. While microfracture can be considered the most cost-effective treatment option for smaller defects, a single-stage tissue engineering procedure can replace ACI to improve the cost-effectiveness for treating larger defects, especially if clinical non-inferiority can be achieved. Copyright © 2016 John Wiley & Sons, Ltd.

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1. Introduction

Damage to the articular cartilage in the knee is a well-recognized and well-documented injury that can cause pain and limitations in both sport-related and daily activities. Currently, treatment aims to regenerate the articular surface and muscle function through various surgical procedures followed by intensive rehabilitation programmes. Arthroscopic cartilage surgeries increase by about 5% each year (McCormick *et al.,* 2014). The rapid growth in the field of tissue engineering and regenerative medicine has resulted in a variety of treatment modalities. Treatment algorithms include microfracture and autologous osteochondral transfer for smaller defects, and allografts or autologous chondrocyte implantation (ACI) for larger (osteochondral) defects (Bekkers *et al.,* 2009b; Cole *et al.,* 2009; de Windt *et al.,* 2012; Behery *et al.,* 2014). In microfracture, fibrocartilaginous tissue repair is stimulated through small penetrations in the subchondral bone plate. The surgical ease, good short-term clinical results, and low costs have made this technique the standard first approach for smaller defects (Bekkers *et al.,* 2009b). However, the durability of the repair tissue and clinical outcome after treatment of larger defects remain causes for concern (Mithoefer *et al.,* 2009). In osteochondral repair, autologous cylindrical plugs, biomaterial scaffolds or allografts are usually implanted in such larger damaged areas (Bentley *et al.,* 2012; Chahal *et al.,* 2013). Autologous chondrocyte implantation is typically used for chondral defects > 2 cm^2 or defects that have failed to respond to microfracture (Mastbergen *et al.,* 2013). In this two-stage procedure, an initial arthroscopy is performed to harvest a biopsy, followed by *in vitro* culture of chondrocytes, and subsequent implantation (Brittberg *et al.,* 1994). Although ACI may result in greater hyaline-like tissue regeneration and durability compared with microfracture, as shown by several randomized controlled trials (Oussedik *et al.,* 2015) and good prospective clinical results up to 20 years after treatment, it is a costly procedure

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requiring two surgical interventions (Peterson *et al.,* 2010a). In-between these two interventions, both the joint homeostasis and the muscle function are usually disturbed (Saris *et al.,* 2003). These limitations have stimulated the development of new single-stage procedures that aim to improve both patient comfort and cost-effectiveness. In recent years, various single-stage procedures have been developed, including microfracture augmentation, scaffold implantation both with and without allogeneic cells or minced cartilage, and stem cell-based cartilage cell therapy (Dhollander *et al.,* 2012a, 2012b; Efe *et al.,* 2012; Anders *et al.,* 2013; Bekkers *et al.,* 2013; de Delcogliano M *et al.,* 2013; Shetty *et al.,* 2013; Stanish *et al.,* 2013; Tompkins *et al.,* 2013; Ahearne *et al.,* 2014; de Windt *et al.,* 2014). However, this rapid 'technovolution' (Mastbergen *et al.,* 2013) has its limitations. For example, there is little room for long-term comparison between these advanced techniques as well as for cost-effectiveness analyses (CEAs). Furthermore, in recent decades, (industry sponsored) clinical trials have mainly focused on clinical outcome and structural repair of the damaged cartilage instead of focusing on health economic evaluations. As a consequence, there is no long-term data available to compare the health economic impact of cell therapy with that produced by microfracture. Given ever-increasing healthcare costs, new technological advancements and stringent insurance company policies, health economic evaluations are an unavoidable development in the field of tissue engineering and regenerative medicine and will increasingly force companies to focus on those products that are most likely to be successful in the market and thereby cost-effective (McAteer *et al.,* 2007; Otani and Baden, 2009). In the present study, an early Health Technology Assessment (HTA) is proposed to predict the cost-effectiveness of an investigator-driven product for single-stage cartilage repair [Instant MSC Product accompanying Autologous Chondron Transplantation (IMPACT), and compare it with both ACI and microfracture] (Ijzerman and Steuten, 2011). This technique is designed to repair cartilage through the immediate transplantation of chondrocytes with their pericellular matrix (chondrons) combined with allogeneic mesenchymal stromal (stem) cells (MSCs) in a fibrin carrier, with the goal of reducing patient discomfort and improving cost-effectiveness (Bekkers *et al.,* 2013). A phase I/II trial (NCT02037204) is currently underway and recently completed the inclusion of the targeted 35 patients. The present health economic model was designed before the initiation of this first-in-man trial to identify key parameters that drive cost-effectiveness, define targets for both product costs and utilities and support further health economic development.

2. Methods

2.1. Study outline

Early health economic modelling was originally applied to predict the likely cost-effectiveness of implementation of IMPACT in clinical practice compared with both ACI and microfracture. The CEA was performed from a societal perspective, meaning that all costs are included from the first consultation to rehabilitation. The model was applied to a cohort of patients (mean age 34 years) with focal cartilage defects eligible for treatment with microfracture, ACI or IMPACT depending on the full availability of data and costs per consultation. This cohort of 40 patients participated in a randomized controlled trial (RCT), which compared the clinical outcome of microfracture and ACI aged 18–50 years with single symptomatic cartilage defects (Vanlauwe *et al.,* 2011). The model also took into account the difference in indication for microfracture (smaller defects) and ACI and IMPACT (larger defects), which is increasingly followed as good practice (Bekkers *et al.,* 2009b). The follow-up period was 5 years, which is the time-horizon of the current model. This time-horizon is considered sufficient to capture the costs and benefits incurred by the treatment alternatives, as treatment failures generally occur within 3 years of treatment (Harris *et al.,* 2011; Gudas *et al.,* 2012; Jungmann *et al.,* 2012a) According to health economic guidelines, future costs and effects must be discounted (Drummond *et al.,* 1997). That is to say that future costs and health gains are weighted in relation to the time at which they occur, with future costs and effects receiving less weight than present ones (Brouwer *et al.,* 2005). In the present study, costs and effects were discounted at 4.0% and 1.5% per annum, respectively, according to currently used guidelines in the Netherlands (Hakkaart-van Roijen *et al.,* 2010).

2.2. Model design

A decision tree was constructed in Excel 2010 (Microsoft, Redmond, WA, USA), as shown in Figure 1. The three alternative treatment options involved IMPACT, ACI and microfracture. Following this first intervention, patients could either be a 'responder' or a 'non-responder'. A patient's response to treatment was defined using the Knee Injury and Osteoarthritis Outcome Score (KOOS) at 60 months. The KOOS is a self-reporting questionnaire providing information on five categories [pain, sport and recreational activities, quality of life (QoL), activities of daily living (ADL) and symptoms/stiffness) for each individual patient that has been validated for cartilage repair (Bekkers *et al.,* 2009a) All five subdomains were scored separately and summed to an overall KOOS score counting from 0 (extreme knee disabilities) to 100 (no knee disabilities). A 'responder' was defined as a patient having an improvement in the overall KOOS score of at least 10%, or an improvement of at least 10% in three of the KOOS subdomains as previously reported to be clinically relevant (Roos and Lohmander, 2003). 'Non-responders' ($<$ 10% improvement in KOOS) may receive a re-intervention, which in the current model is assumed to be microfracture if there is partial graft repair. Responder and non-responder data were derived from the cohort of the RCT database to obtain the transition probabilities of the responders and non-responders after

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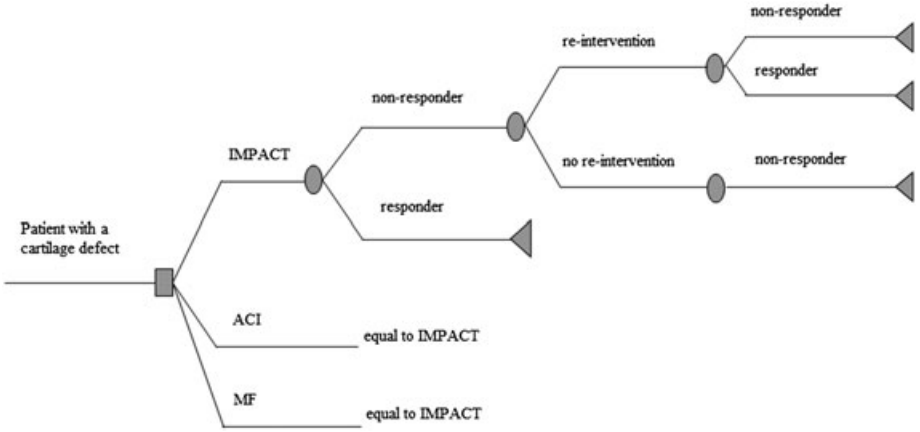

Figure 1. Decision tree. An overview of the various health states a patient can go through after undergoing a first cartilage repair intervention. A responder is defined as a patient showing an improvement of at least 10% in Knee Injury and Osteoarthritis Outcome Score (KOOS) score. A non-responder is defined as a patient reporting less than 10% improvement in KOOS score. ACI, autologous chondrocyte implantation; IMPACT, Instant Mesenchymal stem cell Product accompanying Autologous Chondron Transplantation; MF, microfracture

ACI or microfracture, both with and without undergoing a re-intervention. Transition probabilities for IMPACT were assumed to be equal to the probabilities of ACI. An overview of all transition probabilities is shown in Table 1.

2.3. Utilities and quality adjusted life years (QALYs) gained

Health utility scores were used to estimate the QALYs resulting from the interventions. Scores from the SF-36 health survey were transformed into SF-6D scores to estimate the utility after ACI and microfracture up to 5 years follow-up. The SF-6D is a preference-based health utility index, ranging from 0 (death) to 1 (perfect health), which was used for the purpose of this economic evaluation. As no pre-surgery SF-36 scores were obtained during the trial, the average baseline SF-36 scores were derived from studies presenting pre-surgery SF-36 scores of patients with cartilage defects (Bartlett *et al.,* 2005; Perez-Cachafeiro *et al.,* 2010; Ebert *et al.,* 2011; Schneider *et al.,* 2011; Ebert *et al.,* 2012). The difference in utility between SF-6D scores at baseline and at 5-year follow-up were calculated to determine the clinical effectiveness of both ACI and microfracture. For the single-stage procedure (IMPACT) group, it was assumed that their utility gain equals the utility gain of patients treated with ACI (the non-inferiority assumption). This is based on the early clinical findings from 35 patients recently treated with IMPACT, and the clinical outcome of the first 10 patients at 12 months follow-up, which show a comparable – if not superior – clinical outcome to ACI (unpublished data). To account for possible differences in utility gain, a sensitivity analysis using a 10% range was applied in the model. This range was based on the variation in utility gain after surgical cartilage interventions described in previous reports (Bartlett *et al.,* 2005; Perez-Cachafeiro *et al.,* 2010; Ebert *et al.,* 2011; Schneider *et al.,* 2011; Ebert *et al.,* 2012). For the overall model, QALYs were calculated using the change in utilities over the 5-year window. A linear increase in utility starting after surgery was assumed during the 5-year follow-up period. An overview of the utilities is shown in Table 2.

2.4. Resource use

The average duration of in-hospital stay, number of days sick leave, reduced productivity and physiotherapy consultations were based on administrative data from the University Medical Centre (UMC) in Utrecht, the Netherlands. A summary of all resources used is provided in Table 3.

Table 1. Probabilities of the transitions after interventions

Variable	Probability		
	IMPACT	ACI	MF
Probability of responder after first intervention	0.206	0.206	0.213
Probability of non-responder after first intervention	0.795	0.795	0.787
Probability of non-responder after first intervention, and undergoing re-intervention	0.667	0.667	0.769
Probability of non-responder after first intervention, and not undergoing re-intervention	0.333	0.333	0.231
Probability of non-responder after first intervention, non-responder after re-intervention	0.500	0.500	1.000
Probability of non-responder after first intervention, and responder after re-intervention	0.500	0.500	0.000
Probability of non-responder after first intervention, non-responder after no re-intervention	1.000	1.000	1.000

ACI, autologous chondrocyte implantation; IMPACT, Instant Mesenchymal stem cell Product accompanying Autologous Chondron Transplantation; MF, microfracture).

Table 2. Utilities

Variable	Utility		
	IMPACT (–10.0%; +10.0%)	ACI	MF
Baseline utility	0.690	0.690	0.690
Non-responders after re-intervention	0.779 (0.701–0.857)	0.779	0.774
Responders after re-intervention	0.813 (0.732–0.894)	0.813	0.797
Non-responders without re-intervention	0.745 (0.672–0.820)	0.745	0.740
Responders after first intervention	0.813 (0.732–0.894)	0.813	0.797

ACI, autologous chondrocyte implantation; IMPACT, Instant Mesenchymal stem cell Product accompanying Autologous Chondron Transplantation; MF, microfracture).

Table 3. Overview of resources used

Variable	Value			Reference
	IMPACT	ACI	MF	
Number of days in hospital	2	3	1	UMC Utrecht
Number of days off work	10	15	5	UMC Utrecht
Number of days with reduced productivity	30	40	25	UMC Utrecht
Number of physiotherapy treatments	40	40	40	UMC Utrecht

ACI, autologous chondrocyte implantation; IMPACT, Instant Mesenchymal stem cell Product accompanying Autologous Chondron Transplantation; MF, microfracture); UMC, University Medical Centre.

Table 4. Treatments costs as applied in the model

Variable	Costs			Reference
	IMPACT	ACI	MF	
Materials	€18.75	€18.75	€657.00	UMC Utrecht
Operation theatre	€471.00	€471.00	€355.00	UMC Utrecht
Operation theatre staff	€405.00	€389.00	€267.00	UMC Utrecht
Surgeon costs	€480.00	€480.00	€253.00	UMC Utrecht
Outpatient clinic	€50.00	€50.00	€167.00	UMC Utrecht
Outpatient clinic (MRI, etc.)	€174.00	€174.00	€188.00	UMC Utrecht
Operation theatre	€312.00	€212.00	€136.00	UMC Utrecht
Operation theatre time	€300.00	€295.00	€89.00	UMC Utrecht
Hospital day	€1.280.00	€1.362.00	€82.00	UMC Utrecht
Braces	€115.00	€115.00	–	UMC Utrecht
Product	€3.283.41	€20.600.00	–	UMC Utrecht
Total treatment costs	€6889.16	€24 084.75	€2194.00	UMC Utrecht
Absent from work (day)	€263.26	€263.26	€263.26	Hakkaart-van Roijen *et al.* (2010)
Reduced productivity (day)	€14.97	€14.97	€14.97	Hakkaart-van Roijen *et al.* (2010), Stewart *et al.* (2003)
Physiotherapy treatment	€39.46	€39.46	€39.46	Hakkaart-van Roijen *et al.* (2010)

ACI, autologous chondrocyte implantation; IMPACT, Instant Mesenchymal stem cell Product accompanying Autologous Chondron Transplantation; MF, microfracture); UMC, University Medical Centre.

2.5. Cost parameters

The model incorporates the costs of a hospital stay, treatment, rehabilitation, and the costs of sick leave and reduced productivity. The costs of hospital stay were derived from the costs manual published by Hakkaart-van Roijen *et al.* (2010). This cost manual was also used to estimate the costs per physiotherapy consultation, and the costs of lost productivity at work. The friction cost method was used to calculate the costs of lost productivity. This method estimates the indirect costs of disease, which explicitly considers economic circumstances that limit population losses caused by disease (Koopmanschap *et al.,* 1995). The cost of a day with reduced work productivity was based on a report by Stewart *et al.* (2003) that demonstrated the lost productive time and costs resulting from common pain conditions. The costs of IMPACT, ACI and microfracture were all based on hospital administrative data from UMC in Utrecht. The surgical costs of microfracture represented a single arthroscopy with an inpatient stay of 1 day. The surgical costs of ACI included the first arthroscopy for cell harvesting, the costs of cell expansion and reimplantation surgery during an inpatient stay of 2 days. The costs of the single-stage procedure were calculated by summing the current costs of a single arthrotomy, the costs for the additional surgery time (theatre and personnel) and the calculated costs of the production per IMPACT product. Costs per unit were multiplied by the volume used to calculate the overall costs of care. All costs were converted to 2013 Euros according to the Netherlands consumer prices index. An overview of all costs applied in the model is shown in Table 4.

2.6. Headroom analysis

Headroom calculations were used to explore either the minimum health benefits (or the maximum costs) that are required (or accepted) for an intervention to be cost-effective compared with current practice, at a given societal willingness to pay (WTP) threshold (Yao *et al.,* 2012). This headroom was determined for the IMPACT product compared with both ACI and microfracture, given the expected effect on costs and assuming a range of 10% below and 10% above the expected utility gain (McAteer *et al.,* 2007). A WTP threshold of €30 000 per QALY was used, which is the most commonly applied threshold in the Netherlands, assuming prolonging of the benefits over a 5-year period. Using this threshold, and the differences in QALYs (ΔQ) and costs (ΔC) between IMPACT, ACI and microfracture, the following equation was used:

$$\text{Headroom} = (\ €30\,000 \times \Delta Q) - \Delta C$$

This headroom was subsequently used to calculate the maximum cost of IMPACT compared with both ACI and microfracture.

2.7. Incremental cost-effectiveness ratio and sensitivity analyses

The incremental cost-effectiveness ratio (ICER) was calculated by dividing the incremental costs by the incremental effectiveness (QALYs) for each combination of interventions. The ICER, a cost per benefits/effect unit, allows comparison of cost-effectiveness between interventions (Cohen and Reynolds, 2008). To test how robust the model outcomes are against changes in the input parameters, all input parameters of the model were subjected to one-way sensitivity analyses. This allows the identification of which parameters are the key drivers of both costs and effects, and therefore which parameters should be considered the most important when developing a new product for single-stage cartilage repair. To account for possible differences in the input parameters used in the model, all probabilities and costs were varied with 25% below and above the estimated value. No evidence was found regarding costs per day with reduced productivity. Therefore, a variation of –50% to +200% was applied in the sensitivity analysis. The probability of treatment success was estimated based on the RCT (Vanlauwe *et al.,* 2011), which showed an overall probability of undergoing

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a re-intervention of 13.7% for ACI and 16.4% for microfracture. Results from the RCT showed that the subgroup of patients classified as non-responders after the first intervention (according to their KOOS score) had 67% and 77% probabilities of undergoing a re-intervention for ACI and microfracture, respectively. Because the effectiveness of IMPACT is assumed to be equal to that of ACI, this same percentage was also applied for the patients undergoing IMPACT. Using those probabilities, the probability that a patient would be classified as a non-responder after the first intervention was calculated as 13.7%/67% = 20.6% for ACI and IMPACT, and 16.4%/77% = 21.3% for microfracture.

3. Results

3.1. Model

For the utilities used in this model, ACI showed an increase in QoL score from 0.690 at baseline (where 1 indicates best imaginable health state; Cohen and Reynolds, 2008), to 0.779 or 0.774 at 5 years' follow-up in the responder group (mean increase in KOOS > 10%, or improvement > 10% in three subdomains) for ACI and microfracture, respectively. Five years after treatment, patients in the non-responder group had a utility of 0.745 after ACI and 0.740 after microfracture. The utilities, including those for patients that had received a re-intervention – along with a 10% variation – are shown in Table 2. The total overall treatment costs from the societal perspective are €29 741 for ACI, €11 797 for IMPACT and €6081 for microfracture (Table 4). Of those total costs, societal costs (involving costs for absence from work, physiotherapy and loss of productivity) involved €6126 for ACI, €4660 for IMPACT and €3269 for microfracture.

3.2. Headroom analysis

For a change in QALYs of IMPACT compared with ACI of –10%, 0% and 10%, this analysis results in a headroom for IMPACT of €23 697, €29 741 and €35 786 respectively. Compared with microfracture, the headroom for IMPACT is €–10 598 (–10%), €–4553 (0%) and €1491 (+10%). The calculations assume a WTP of €30 000/QALY. With the costs of IMPACT estimated at €11 797, all headroom and accompanying maximum prize calculations are provided in Table 5.

Table 5. Headroom

Change in utility IMPACT	IMPACT vs. ACI	IMPACT vs. MF	Maximum price, IMPACT vs. ACI	Maximum prize, IMPACT vs. MF
–10%	€11.899	€–10.598	€23.697	€1199
0% (base case)	€17.944	€–4.553	€29.741	€ 7244
+10%	€23.989	€1.491	€35.786	€13 289

ACI, autologous chondrocyte implantation; IMPACT, Instant Mesenchymal stem cell Product accompanying Autologous Chondron Transplantation; MF, microfracture).

3.3. Incremental cost-effectiveness analysis

The difference in societal costs between IMPACT and ACI and microfracture are €–17 944 and €5716 respectively, while the additional costs of ACI compared with microfracture are €23 660. The difference in QALYs gained is assumed to be zero for IMPACT vs. ACI (non-inferiority), while the difference in QALYs for both IMPACT vs. microfracture, and ACI vs. microfracture is 0.04 over the 5-year time-horizon. This results in an ICER of IMPACT vs. microfracture of €147 513 per QALY gained, and an ICER of €610 600 per QALY gained for ACI vs. microfracture.

3.4. Sensitivity analyses on model input

A one-way sensitivity-analysis was performed to evaluate the impact of changes in input parameters on the accompanying ICERs, for both ACI vs. microfracture (Figure 2) and IMPACT vs. microfracture (Figure 3). The results of this one-way sensitivity analysis indicate that the ICER is most sensitive to changes in the costs of the product. However, even a strong decrease in the costs of the ACI product (from €20 600 to €4 000) still results in an ICER for ACI vs. microfracture of approximately €200 000/QALY, which is far above the generally accepted cost-effectiveness thresholds. Other parameters that affect the total societal costs are mainly the probability of being a non-responder (either after the first intervention or after a re-intervention) and, to a lesser extent, the costs of absence from work, the costs of reduced productivity and the costs of physiotherapy.

3.5. Influence of defect size and non-inferiority assumption on the ICER

It is known from the literature that microfracture is less effective at treating large cartilage defects (Bekkers *et al.,* 2009b; Saris *et al.,* 2014). Therefore, when assuming that a patient has a large cartilage defect (> 2.5 cm^2), a lower utility might be expected when such a patient is treated with microfracture (Roos and Lohmander, 2003). In addition, there is limited evidence available concerning the utilities after undergoing IMPACT, suggesting high uncertainty in this input parameter. Therefore, a two-way sensitivity analysis was performed to evaluate the simultaneous effect of changes in both the utilities after IMPACT and microfracture on the ICER (Figure 4). This figure shows that a 4% decrease in the utilities after microfracture, combined with a 4% increase in the utilities after IMPACT, is expected to make IMPACT a cost-effective treatment option at a WTP of €30 000/QALY.

Assuming that IMPACT would be precisely as effective as ACI is unrealistic, therefore the effect of both a 10% increase and a 10% decrease in the utility after undergoing IMPACT was evaluated. Assuming a 10% decrease in all utilities after undergoing IMPACT, the ICER would be €89 057/QALY. This suggests that IMPACT would be less effective, but also less expensive than ACI. Thus, it would depend on society's willingness to accept a small decrease in

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Parameter	Change	Lower limit	Upper limit
Costs of the product	€4,000 – €20,600	€198.672	€610.600
Probability of non-responder after 1st intervention	+/–25%	€545.069	€692.668
Probability of re-intervention + non-responder after 1st intervention	+/–25%	€682.612	€553.098
Costs per day absent from work	+/–25%	€585.026	€636.174
Number of days off work after 1st intervention	+/–25%	€586.102	€635.099
Cost per day with reduced productivity	–50% and + 200%	€602.557	€642.772
Costs of physiotherapy treatment	+/–25%	€599.518	€621.683
Number of physiotherapy treatments after 1st intervention	+/–25%	€600.808	€620.393
Number of hospital days after 1st intervention	+/–25%	€602.660	€618.541
Number of days with reduced productivity (first intervention)	+/–25%	€606.885	€614.316

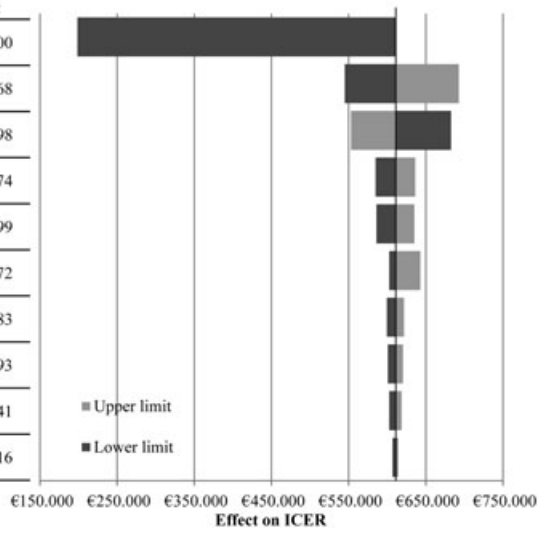

Figure 2. One-way sensitivity analysis on input parameters of autologous chondrocyte implantation (ACI) vs. microfracture. The result of changes in input parameters on the incremental cost-effectiveness ratio (ICER). Only the input parameters that most strongly affect the ICER are shown. Because of the limited availability of data concerning the costs of reduced productivity after undergoing ACI or microfracture, this input parameter was changed by –50% and +200%

Parameter	Change	Lower limit	Upper limit
Costs of the product	€1,283 – €10,000	€97.883	€314.185
Probability of non-responder after 1st intervention	+/–25%	€128.636	€171.152
Costs per day absent from work	+/–25%	€130.105	€164.921
Number of days off work after 1st intervention	+/–25%	€131.180	€163.845
Cost per day with reduced productivity	–50% and + 200%	€141.328	€172.253
Probability of re-intervention + non-responder after 1st intervention	+/–25%	€161.097	€136.666
Costs of physiotherapy treatment	+/–25%	€136.430	€158.595
Number of physiotherapy treatments after 1st intervention	+/–25%	€137.720	€157.305
Number of hospital days after 1st intervention	+/–25%	€139.572	€155.453
Number of days with reduced productivity (first intervention)	+/–25%	€144.726	€150.299

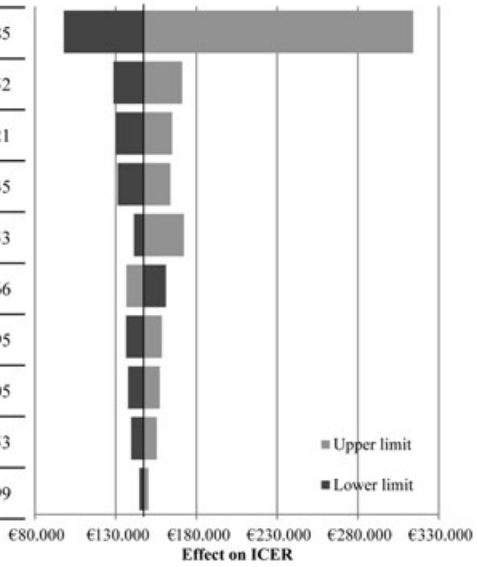

Figure 3. One-way sensitivity analysis on input parameters of Instant MSC Product accompanying Autologous Chondron Transplantation (IMPACT) vs. microfracture. The result of a changes in input parameters on the incremental cost-effectiveness ratio (ICER). Only input parameters that most strongly affect the ICER are shown. Because of the limited availability of data concerning the costs of reduced productivity after undergoing autologous chondrocyte implantation (ACI) or microfracture, this input parameter was changed by –50% and +200%. In addition, to compensate for the higher uncertainty concerning the estimation of the product costs of IMPACT, a variation in product costs of €1283 to €10 000 was applied

QoL to save €17 944 per patient. Conversely, if the utility after undergoing IMPACT proves to be 10% higher than after undergoing ACI, the ICER will be €–89 057/QALY. In this case, IMPACT would then be superior to ACI by being both a less costly and a more effective treatment option.

Discussion

The most important finding of the present study is that in the mid-term follow-up (5 years a single-stage procedure (IMPACT) can be superior to ACI in terms of cost-effectiveness. Although ACI has demonstrated encouraging clinical results up to 20 years after surgery, RCTs have failed to show its superiority over microfracture (Peterson *et al.,* 2010b; Lim *et al.,* 2012; Negrin and Vecsei, 2013). This is especially relevant as the current healthcare reforms and cost reductions driven by insurance companies limit the scope for expensive cell therapy. Indeed, a recent systematic review emphasized the paucity of CEA studies in sports medicine (Nwachukwu *et al.,* 2014). For cartilage repair, two studies were identified that described a CEA for ACI. In one cohort of 44 patients, an estimated

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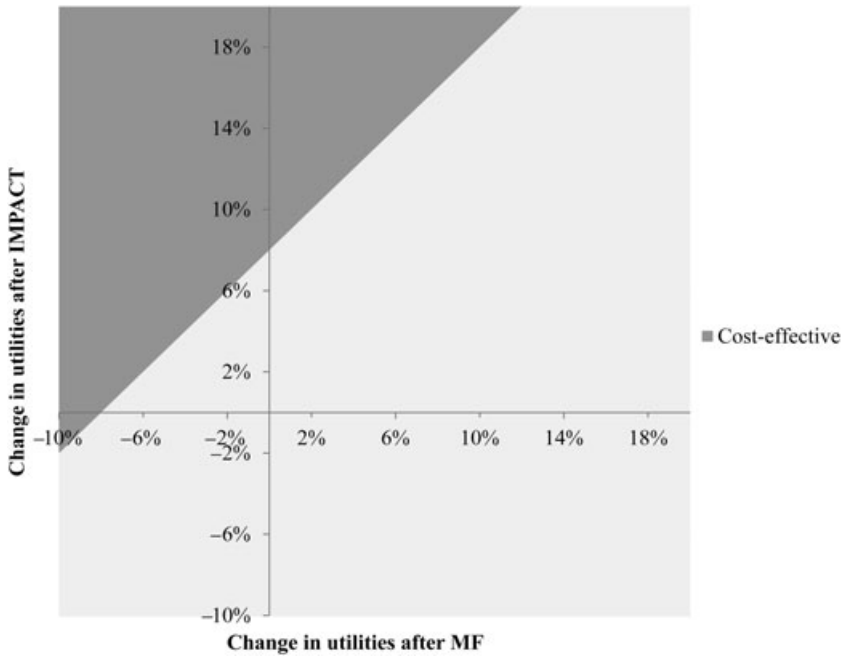

Figure 4. Two-way sensitivity analysis on input parameters of Instant MSC Product accompanying Autologous Chondron Transplantation (IMPACT) vs. microfracture. Changes in utilities after undergoing either microfracture or IMPACT. The dark tinted area represents a combination of changes in input parameters that make IMPACT a cost-effective treatment option compared with microfracture at a willingness to pay (WTP) of €30 000/Quality Adjusted Life Year (QALY)

cost of $6791 per additional QALY was predicted, while in another economic study, which compared both the periosteal patch and the collagen cover for ACI, costs per QALY were estimated to be $9466 and $9243, respectively (Minas, 1998; Samuelson and Brown, 2012). Although these findings are encouraging, the first study only used a 12-month follow-up period. Therefore, the significant increase in utilities may have been an overestimation when compared with clinical trials that have a longer follow-up period (as seen in the present RCT). The second study produced a costs per QALY ratio, rather than an ICER in comparison with a WTP threshold. Thus, as suggested by the above-mentioned systematic review (Nwachukwu *et al.,* 2014), there are opportunities for methodological improvements in terms of economic analyses for both existing and proposed techniques. Currently, start-up companies are increasingly faced with the difficulty of demonstrating whether the improvement promised by a new product would justify the additional costs (McAteer *et al.,* 2007). However, an early HTA can contribute to estimating the cost-effectiveness of such a new product before implementation in clinical practice. This can be vital in guiding both future research and product development, as discouraging results from an early HTA may prevent expensive animal and clinical testing. However, it should be acknowledged that patients included in these models, which are often based on RCTs, are not always typical of patients seen in orthopaedic sports practice (Engen *et al.,* 2010). For example, clinical experience suggests that failed cartilage repair treatment is difficult to model, as patients have often undergone several procedures and because surgeons have limited treatment options after a failed ACI (Engen *et al.,* 2010). In addition, although the RCT used in the present study reported similar outcomes for microfracture and ACI, it has been shown that larger defects tend to respond better to ACI (Bekkers *et al.,* 2009b) Moreover, ACI is commonly used as a second-line or salvage procedure following failed marrow stimulation, because repeated microfractures have a higher tendency to fail (de Windt *et al.,* 2012; Truong *et al.,* 2014). Thus, as shown in the present CEA, using a single-stage procedure with similar outcome but reduced costs compared with ACI, while achieving superior outcome compared with microfracture for larger defects, may improve the cost-effectiveness and subsequently the availability of such treatments. It is stressed that this model is aimed at predicting future cost-effectiveness, which may differ from country to country and depend on the policies of insurance companies. In this early HTA, various environmental factors such as the influence on absence from work, overall product costs and the costs of rehabilitation have also been taken into account. Again, when considering larger defects, or those that require a salvage procedure, a single-stage procedure that can replace a significantly more expensive ACI procedure can be considered the most cost-effective treatment option (Negrin and Vecsei, 2013). For this single-stage procedure (IMPACT), a headroom analysis showed that the maximum costs of IMPACT may be increased up to €29 741 when IMPACT proves to be as effective as ACI. If the utilities of IMPACT were 10% lower than ACI, the maximum costs of IMPACT would be €23 697. With the costs of a single-stage procedure not exceeding these amounts, and the preliminary findings of the phase I/II trial, which show short-term safety and good clinical improvement, this could mean that a significant reduction in costs might be achieved for patients who are currently treated with ACI without compromising patient outcomes.

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Indeed, early findings of the phase I/II trial show clinical improvement of all 35 patients at 1 year, which is similar to or superior to 1-year results after ACI. (unpublished data). For example, if a knee surgery centre performed 50 ACIs per year, replacement of ACI by a single-stage procedure could save up almost €900 000 (about €18 000 per treatment) in 1 year while achieving similar clinical outcomes or even up to a 10% improvement. However, the sensitivity analysis showed that if the utilities after undergoing IMPACT prove to be 10% lower than after ACI, the WTP threshold would be exceeded. This sensitivity analysis also suggested that it is mainly the utility of patients after the first intervention that strongly affects the treatment's overall cost-effectiveness. While 5 years can be considered a short follow-up period, it has previously been shown that if a cartilage repair treatment fails, this tends to occur within 2 years of the procedure, making a 5-year period sufficiently long to determine the medium-term success rate of treatment (Harris *et al.,* 2011; Gudas *et al.,* 2012; Jungmann *et al.,* 2012b).

According to the one-way sensitivity analyses, the costs of the cartilage repair procedures had a strong effect on the model outcome (ICER). Using the same cohort as in the current study, Gerlier *et al.* (2010) predicted that cell therapy would be superior in terms of both costs and long-term QALY gain, while it would also reduce the uncertainty of developing osteoarthritis (OA). Here, we show that a reduction in costs and improvement in QALYs can be achieved through replacement of ACI by a single-stage procedure (assuming a high probability of non-superiority). However, it should be mentioned that Gerlier *et al.* (2010) assumed that there is a good correlation between high-quality cartilage repair and OA avoidance later in life. Data showing correlation between repair tissue quality and both clinical outcome and its long-term effect on the development of OA is lacking. Given the fact that microfracture has shown excellent results at the mid-term follow-up, the present model emphasizes the possible role of this treatment modality in long-term cost-effectiveness, especially as a first-line treatment for smaller defects. Again, predicting the long-term effects on the development of OA on the basis of tissue quality is difficult. Therefore, the findings of the present study may better reflect the predicted effects of microfracture, ACI and a single-stage procedure (IMPACT) on cost-effectiveness than previous work.

In recent years, cell-free single-stage procedures have been developed to augment microfracture by improving the repair tissue quality, thereby achieving clinical outcomes comparable to those obtained with ACI (Filardo *et al.,* 2013). Recently, a microfracture augmentation technique using a chitosan-based polymer scaffold was found to yield a possible long-term cost-saving when compared with ACI, especially for larger defects (Frappier *et al.,* 2014). A randomized controlled trial comparing this technique with microfracture showed promising results in terms of defect fill and magnetic resonance imaging-assessed repair tissue in favour of microfracture augmentation (Stanish *et al.,* 2013). However, the short-term follow-up and the small defect size used in both groups (2.32 cm^2 for microfracture augmentation and 1.95 cm^2 for microfracture), along with the comparable clinical outcome shown in both groups, raise the question of whether microfracture augmentation can successfully replace cell therapy, particularly for larger defects (Filardo *et al.,* 2013; Khazzam, 2013).

One possible advantage of using a single-stage procedure compared with a two-stage procedure is the effect on absence from work. Disability and work absence are important factors in economics, especially in young and active patients undergoing cartilage repair (Lindahl *et al.,* 2001). It has been shown that ACI is capable of having a cost-saving effect 10 years postoperatively based on reduced work absence and disability (Lindahl *et al.,* 2001). In the present CEA, the post-procedural societal costs for work absence, physiotherapy and loss of productivity for microfracture and IMPACT were €3269 and €4660, respectively, compared with €6126 for ACI.

Recently, a long-term retrospective CEA on early anterior cruciate ligament (ACL) reconstruction, rather than rehabilitation and delayed reconstruction, found reduced rehabilitation costs and superior quality of life gain for the early treatment arm (Mather *et al.,* 2014). Early HTA may contribute in estimating those costs in the early stages of product development, to allow early prediction of the cost-effectiveness of a new intervention compared with current practice.

This study included only a small number of patients from a RCT with a follow-up of 5 years. Greater patient numbers and a longer follow-up period will make such an early HTA more reliable, especially once the effects of such cartilage repair procedures on the long-term development of OA become evident. Furthermore, the effectiveness of the single-stage procedure is assumed based on early findings of a phase I/II trial and may not represent its long-term outcome. However, it should be emphasized that an early HTA aims to model the effect on cost-effectiveness as part of a new strategy which aims to set targets for advanced-therapy medicinal product (ATMP) development and implementation. Although a single RCT was used, the clinical outcome is consistent with similar trials performed.

For the present study, all costs were derived from the hospital administration data and/or from other Dutch data resources, which may limit its transferability to other countries. Nevertheless, while differences in costs undoubtedly occur between countries, comparable cost-reduction ratios can be expected because there are large differences in costs between the different interventions.

This work provides insight into the effect of outcome parameters such as absence from work, early clinical outcome and product costs, and on the total societal costs for each treatment option. Based on the current CEA, these parameters have been added as outcome measures in the ongoing IMPACT trial along with QoL assessments. This will allow for a reliable future evaluation of both cost-effectiveness and model accuracy. In addition, it has indicated which parameters are important in determining

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the cost-effectiveness of a new treatment option compared with that of current practice.

In conclusion, this is the first study to show that a single-stage procedure can be cost-effective in the mid-term follow-up compared with ACI. Although microfracture can be considered the most cost-effective treatment option for smaller defects, a single-stage procedure may replace ACI to improve the cost-effectiveness for larger defects, especially if non-inferiority can be achieved. Important parameters in the model appear to be the costs of the product, absence from work, reduced productivity and physiotherapy costs. Future analysis and long-term follow-up will reveal whether a single-stage procedure can indeed improve cost-effectiveness compared with ACI, based on these input parameters and the proven accuracy of the model.

Conflict of interest

The authors declare that there is no conflict of interest.

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