A preliminary early economic assessmentof a novel BM-MSC secretome based therapy for Osteoarthritis patients

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Abstract

Mesenchymal Stromal Cells (MSC) derived secretome has been shown to have immunomodulatory and regenerative properties. Thus, and based on animal studies, MSC-derived secretome could become a potential biotherapeutic for managing Osteoarthritis (OA) of the knee. This work aims to contribute to the research and development of biotherapeutics. For this purpose, an early Health Technology Assessment (eHTA) is established, allowing to consider different cost and effectiveness scenarios, to support stakeholders informed decisions. The cost of goods (CoGs) per dose of biotherapeutic is calculated on the basis of biological, economic and manufacturing process parameters, through the implementation of Monte Carlo simulations. The biotherapeutic's CoGs are used in the Cost Utility Analysis (CUA). CoGs are combined with WOMAC (pain, function, and rigidity) scores, which are then converted to quality adjusted life years (QALY). A Multicriteria Decision Analysis (MCDA) has been initiated to complement the CUA, since the latter does not provide all the relevant information for decision making. The results suggest that for a scenario where the new therapy proves to be twice as effective (0.8 QALY per patient) as the current therapy - Autologous Protein Solution (APS) (0.4 QALY), and demonstrate a 75% reduction in CoGs per patient, it can be said that the biotherapeutic will dominate the existing therapy. This thesis will help to design scientific studies, indicating how to reduce the costs of the new biotherapeutic, and contribute to an improvement in the health care of OA patients.
Keywords: Osteoarthritis, Regenerative medicine, Mesenchymal stromal cells, MSC-derived secretome, Monte Carlo simulations, early Health Technology Assessment, Cost-Utility Analysis

1. Introduction

Osteoarthritis (OA) is considered a "wear and tear" disease and its progression ends up in cartilage destruction, subchondral bone remodelling, and inflammation of the synovial membrane [1]. Nevertheless, it is believed that OA is not a single disease, but rather a final stage of joint tissue destruction, involving inflammation, which does play an important role in OA's evolution [1]. OA non-invasive treatments have been proposed to avoid or delay the need of total joint replacement, which is the final procedure performed in those cases [2]. According to WHO [2], it is estimated that by 2050, there will be 2 billion people aged over 60 years old. Consequently, the global incidence of OA will increase. 130 million people worldwide will be affected by OA, and almost a third of these, around 40 million will be severely crippled [2]. Nevertheless, the concern does not account only for patients themselves but also for the significant associated economic burden. This thesis evaluates the possible use of a MSC secretome based therapy for knee OA. This suggestion is based on the collection of the following pre-clinical evidences: (i) After seven days, there was a reduction of pain and cartilage repair improvement for MSC secretome compared to the control, in a murine OA model [3]. (ii) By twelve weeks, defects treated with exosomes have demonstrated an improved gross appearance and improved the histological score in comparison to the control group [4].

2. MSC-derived secretome vs APS

The MSC-derived secretome is comprised by bioactive factors (nucleic acids, soluble proteins, and lipids) produced by MSC that are secreted to the extracellular space as soluble and/or as encapsulated in Extracellular Vesicles (EV)s [5, 6, 7]. The use of the secretome, rather than MSC, as therapeutic agent in regenerative medicine [8, 9, 10], presents two main advantages. The first one is related with avoiding safety concerns associated

with cellular contamination, potential presence of oncogenic cells and uncontrolled cell division [8]. Secondly, the effect of exosomes-based therapy is transitory, since the presence of exosomes is not permanent and they can be eliminated in case of adverse effects. The small size of exosomes can contribute to a lower immunogenicity or toxicity than when using artificial carriers [8, 9, 10]. Additionally, the manufacture of exosomes allows process optimization and clinical up-scaling, ensuring reproducibility and cost- effectiveness [9]. This allows a controlled selection of cell sources and the possibility of adopting cell lines with unlimited expansion potential resulting in a higher yield of the final therapeutic product [9, 10]. Contrarily to cells, when exosomes are used as therapeutic agents, safety, dosage, and effectiveness can be assessed using methods similar to the ones used for conventional pharmaceutical agents [9, 8]. This can significantly speed up the adoption of such novel therapies to clinical practice. Additionally, purified exosomes can be stored for longer periods without loss of their biological activity [9, 8]. Several research studies provide encouraging data to suggest the use of MSC-derived EVs to treat joint injury and OA [8].

APS is a therapy prepared from autologous peripheral blood, which is composed of white blood cells (WBCs) containing anti-inflammatory proteins, platelets containing anabolic growth factors, and concentrated plasma containing anti-inflammatory proteins [11]. The blood sample, after to be collected, is incubated with glass beads and centrifuged, which increases IL-1Ra production, along many other cytokines, and anabolic growth factors such as epidermal growth factor (EGF), vascular endothelial growth factor (VEGF), IGF, TGF-β and anti- inflammatory cytokines of soluble tumor type II (sTNF-RII), IL-4 and IL-10 [12]. Thus, in APS therapy is obtained high concentrations of anti-inflammatory cytokines and growth factors from peripheral blood samples of compatible donors or the patient, exploring the interaction of the various components [12].

The study perspective to be adopted is one of the initial decisions to be taken when conducting an eHTA, as it determines which costs are deemed relevant, affecting the remaining assessment. Secondly, a comparison of two or more health alternatives must be made. Additionally, to perform the assessment it is necessary to have a comparator i.e. a cost-effective alternative usually used therapy, to compare the inputs (costs) and outputs (consequences) associated with each of the alternatives. Thirdly, the evaluation also requires an adequate length of follow-up to fully evaluate the impact of the ATMP [13, 14].

3. Methodology

This works aims to investigate the health-economic value of introducing an envisaged MSC-derived secretome therapy for OA relief. The eHTA targets HTs that is still in an early research and development stage, that information and knowledge about manufacture is also scarce, implying to make a variety of decisions and assumptions throughout the study [15]. Therefore, the process of manufacturing the biological therapeutic is described and designed according to a given set of literature-based assumptions [15].

The idea of the present work is to transpose the information on animal studies [4, 3] which already have scientific evidence to individuals. The estimation of manufacturing costs is obtained through Monte Carlo simulations to incorporate biological uncertainty and considering that the manufacture process has not yet been developed. The estimated manufacturing costs of MSC-secretome therapy are used into a CUA. APS is used as comparator therapy. The current study is focused on informing on a clinical trial phase II, designed to include 200 patients administered with the envisaged therapeutic agent. In a first approach, as central scenario, the CUA will be performed to evaluate whether there are (or not) incremental benefits assuming health outcomes to these therapy similar to the ones reported for patients administered with APS therapy [16, 17, 18]. Based on such model, a cost-effectiveness comparison will then be formulated (MSC-derived secretome against APS). After that, a MCDA model was formulated To considering aspects not previously captured in the CUA model. Figure 1 portrays a general insight of the timeline of the various models that comprise the methodology of this thesis.

To establish manufacture process model it was defined different stages needed to the production of the new desired therapeutic product, composed of a protein cocktail. A Monte Carlo approach was used to compute the model variables to integrate on the model the variability associated with the biological variables (namely cell growth behaviour). An outline of the manufacturing process can be seen below - Figure 2, starting with the upstream phase, following DSP, and ending at the final phase of ATMP, ready for administration into the individuals.

In order to more accurately describe the diverse biological behaviour and to take into account uncertainty (to a certain degree) the present work portrays a stochastic cell growth model. To achieve this, in the absence of a distribution of values for growth rates, but only having access to key parameters, such as range and mean values, a triangular distribution was used - Table 1 [19]. Triangular

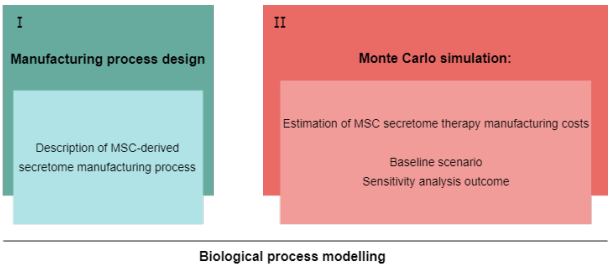

Figure 1: Overview of all sub-models sequence present in this chapter. I-Description of manufacturing process, II-Monte Carlo simulation, III-CUA model, IV-MCDA model.

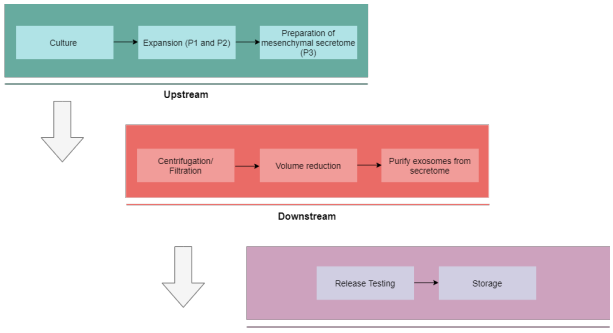

Figure 2: Process diagram with the main stages of MSC secretome therapy manufacturing.

distributions are used when the shape of a given distribution of a variable is unknown.

Table 1: Mean cell growth rate per passage.

No. of Passage	μ
1	0.52 (0.32-0.61)
2	0.48 (0.29-0.71)
3	0.48 (0.27-0.49)

$$\frac{dX}{dt} = \mu X \Leftrightarrow \frac{dX}{X} = \mu t \Leftrightarrow X = X_0 e^{(\mu(t-t_0))} \quad (1)$$

- X_0 - represents the initial number of cells.
- μ - represents the growth rate which can vary depending on the passage (see Table 1)
- t-t_0 - time difference between the day when the number of cells is being analysed and the initial instant.

In this section, a diagram with key parameters highlighted is presented in order to proceed with the analysis - see Figure 3.

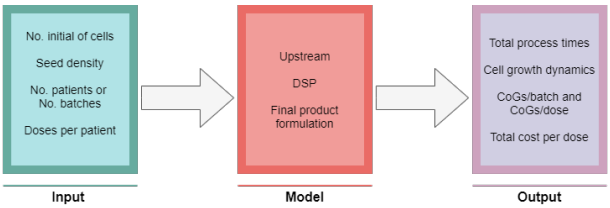

Figure 3: Relevant inputs and outputs of the model.

In order to model the process of producing a therapeutic, a stochastic model, resorting to Monte Carlo simulations, was developed. Some aspects are based on TESSEE [19], however many features differ from TESSEE configuration. The objective of these calculations is to estimate the CoGs per dose of the MSC-derived secretome therapy to estimate the price dosage, which will be applied on the CUA model.

Cell expansion, exosome production, downstream processing and final product formulation stages costs were estimated [19]. Biological and costs related variables are tracked during simulations, allowing to assess and record values of the whole duration of each simulation [19].

The Monte Carlo model has been configured for the therapeutic manufacturing process starting with an initial number of cells (sourced from donors) and seeded at an optimal initial density on the selected ET. The number and type of ET units are selected to minimization of the cell expansion stage cost. Note that given an initial seeding density several combinations of ETs are possible to be attained. Therefore, ET selection is done through an algorithm which reduces the cost and quantity of ETs to be exploited during the process.

A confluence time of 5 days was established for the cell expansion stages. The model calculates the needs in culture medium feedings [19], i.e. renewal of the medium in each T-flask. A yield of 90% is assumed at the end of the 3 passages considered in this work [19].

Thereafter, the model simulates the separation of the conditioned medium (secretome) from the cells, which in turn undergoes successive centrifuging, washing and volume reduction steps to purify the exosomes apart from media components and prepare them for final product (see DSP description). A yield of 80% is considered here, causing 20% of the exosomes to be discarded and fail to pass to the next stage [19].

The production process continues the needed times until the target number of exosomes (or doses, equivalently) is met.

The final product is then formulated and cryopreserved after passing a quality control stage. This is a step which is required to verify if the therapeutic complies with all regulations defined by laboratory

standards, making sure that the results are consistent, safe and suitable for human use [19].

The stochasticity incorporated in the current model captures the biological behaviour of cells grow, observed in real conditions. Therefore, the estimations portray more accurately the variability of possible outcomes. The stochastic model here presented follow a triangular distribution of P1 and P2 cell growth (Table 1) and the probability of product release of 90% (Table 3).

The costs incurred presented in this work are taken from literature in USD and then converted into EUR according to the currency exchange rates [20].

Table 2: GMP facility and equipment related parameters.

Parameter	Value	References
Area of GMP facility	400 m^2	[21]
No. of workers	1	[21]
No. of incubators	2	[21]
No. of BSCs	1	[21]
No. of centrifuges	2	[21]
Fraction of clean room space	20%	[19]
Price of clean room/ m^2	4,908.41€	[19]
Price of non clean room/ m^2	2,863.17€	[19]
Daily worker pay	84.41€	[19]
Price of unit incubator	15,054.40€	[19]
Price of unit BSC	14,349.60€	[19]
Price of unit centrifuge	10,129.10€	[19]
Annual cost of CO_2 supply	5,064.57€	[19]
Annual cost of other gases supply	13,167.90€	[19]
Annual cost of additional lab supplies	6,668.35€	[19]
Annual cost of requalification	55,203.80€	[19]
Annual cost of maintenance	44,568.20€	[19]
Annual cost of cleaning	23,634.70€	[19]
Annual cost of garments	1,688.19€	[19]
Equipment depreciation period	5 years	[19]
Facility depreciation period	15 years	[19]

Table 3: Cell processing parameters.

Parameter	Value	References
Common across stages		
Culture media supplement/ml	0.628€	[22]
DPBS/ml	0.056€	[23]
TrypLE (Harvesting agent)/ml	0.09€	[19]
Expansion		
Maximum no. passages	3	[19]
Seeding density/passage (cells/cm^2)	3000	[19]
Time to confluence (days)	5	[19]
Harvesting yield	0.9	[19]
Harvesting time	14 min	[19]
Downstream processing		
No. of washes	2	[19]
Volume reduction and washing time	4h	[19]
Volume reduction yield	0.8	[19]
Fill finish time	2h	[19]
Cryovial volume	2mL	[19]
Unit price cryovial	1.1€	[19]
Cryomedium/ml	2.3€	[19]
Ratio cryomedium/basal medium	0.5	[19]
Final product formulation		
Pass/release ratio	0.9	[19]
Price quality control testing/batch	8,441.95€	
Time release testing	2h	[19]
Cleaning up		
Preparation time for the next batch	2h	Assumption

In the section of Economic modelling two levels of action were defined, methods covering CUA and MCDA. Firstly, the costs required to set up a CUA were estimated through Monte Carlo simulation (concerning MSC-derived secretome therapy) and based on literature (concerning APS).

In order to obtain the outcomes of the therapy, QALYs were not directly measured, instead WOMAC scale was used in accordance to literature's patients benefits [16, 18]. Then it was converted to utilities in the form of EQ-5D, which is a standardised instrument able to measure the health status of an individual or a sample of individuals. This conversion was achieved through a web tool provided by Wailoo et al. [24] requiring a WOMAC data set as input, defined by the user. EQ-5D scores which depend on age and gender of the data set patients are obtained.

Moreover, several levels of screening were performed in order to capture various possible scenarios. Given that eHTA is a study carried out in an environment of uncertainty which, in this case, the therapy has not yet been approved, and in which hypothetical benefits are assumed, it is useful determining how the variation of a given parameter is reflected in the process, and in turn in supporting decision making. There are other aspects besides CUA that are considered in decision-making in several countries. In this way, a MCDA model is structured to help visualising the extent to which the CUA considers all relevant aspects to the assessment. This prepares a framework for when reliable MSC-derived secretome data is available to make use of it and draw the appropriate conclusions.

4. Results & discussion

Monte Carlo simulations - Baseline scenario

A baseline scenario was simulated, using Monte Carlo simulations type (sub-model II), to calculate the costs to obtain the MSC-derived secretome doses, following the envisaged manufacturing process, needed to support a phase II of a clinical trial. The results on-wards presented were obtained after running the model for 100 runs for each case scenario - Table 4. It was observed that, by performing several sets of simulations, a higher number of simulations would not translate into better confidence intervals nor change the mean value of most variables. Therefore, having a higher number of simulations would only contribute for longer model run times, i.e. for 100 runs the simulation time was around 4 minutes, for 1000 was approximately 40 minutes and finally for 10000 runs it took approximately 22 hours, meaning that it would only increase the time that the model is running without adding significant changes to the results, while having to wait more time for the results do be produced. The main selected inputs to the model were $1x10^5$ for the initial cell number and a seeding density of 3000 cells/cm^2 - Table 3. For clinical expansion, it is unfeasible to use very low seed densities

since it translates into higher times-to-confluence, higher frequency of medium changes and more ETs utilisation - about 75% of the most recent clinical trials use a seeding density of 3000 cells/cm^2 to further reduce the cost/work trade-off [19].

'random' stands for simulation type in which cell growth rate was modelled by a triangular distribution and 'fixed' stands for simulation type in which it was not used a distribution of values for cell growth rates but instead only the mean values.

Table 4: Simulation parameters of the first level of screening according to prob0 simulation type.

Parameter	Random	Fixed
No. cells at P3/Batch	1.55x10^7	1.34x10^7
No. final exos/Batch	7.8x10^9	6.64x10^9
Doses/Batch	58.45	49.8
Patients/successful Batch	12.9	11.2
Batches to obtain target Patients	17.84	20.24
Batch duration (days)	15.57	15.55
Process duration (days)	277.77	314.76
ETs:		
P1	2 $Tflask25$	2 $Tflask25$
P2	2 $Tflask225$	2 $Tflask225$
CoGs/Batch	21,380.4€	21,295.79€
CoGs Expansion/Batch	351.99€	298.1€
CoGs DSP/Batch	230.28€	199.52€
CoGs FPF/Batch	8,441.95€	8,441.95€
CoGs/Dose	367.59€	429.35€
CoGs/Patient	1,837.95€	2,146.75€

Table 4 shows the summary output of the analysis considered as the baseline scenario. It is important to note that the values shown in Table 4 correspond to the average values per run, in a total of 100 runs.

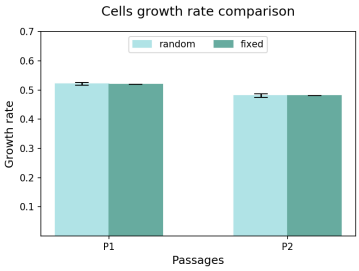

Figure 4: Mean of growth cell rate.

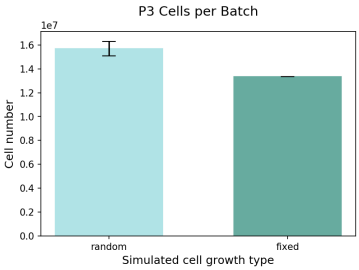

Figure 5: Cells after the expansion of the passage 3.

In agreement with Figures 4,5 and 6, a set of outputs related to the biological side of the process is portrayed. Overall, analysis after simulations

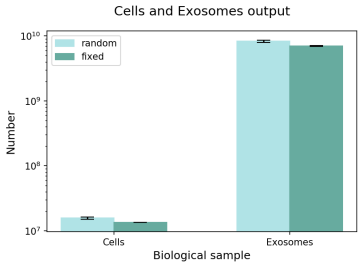

Figure 6: Cells at the end of Expansion and Exosomes estimated output by the end of DSP.

shows that 'random' simulation type yield higher number of cells than the 'fixed' simulation type - Figure 5. This result is related to the exponential relation between the cell number and growth rate. Therefore, using a triangular distribution of cell growth rates with the same mean value as the growth rate used for the 'fixed' simulation type - Figure 4, generates a higher cell number outputs. An exponential does not preserve the linear relationship observed between the arguments – cell growth rates – so, by using a triangular distribution of cell growth rates with the same mean value will result in a higher distribution of obtained cells in comparison to using only a deterministic value – 'fixed' simulation type, despite having the same mean values for both simulation types. Figure 6 results are in accordance to the modelled condition that each cell will contribute with around 700 exosomes to the secretome.

Literature points out that the 'pass release ratio' on quality control testing is about 90% [19]. In this step a dose is sacrificed to be tested against the required criteria of quality [19]. When a batch does not pass the quality control testing, all doses of such batch are discarded, but its production cost still need to be incorporated on total dose costs [19].

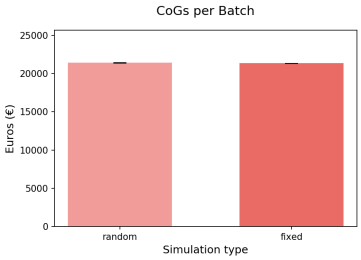

Figure 7: Direct and indirect CoGs per Batch.

Figure 7 shows the total CoGs per Batch for each simulation type 21,380.5€ and 21,295.8€ ('random' and 'fixed' respectively).

Figure 9 portrays the CoGs per Batch of Figure 7 broken down into resource categories, which means that the sum of the bars of Figure 9 makes up the CoGs per Batch of Figure 7, for each simulation type. Figure 8 shows consumables, reagents,

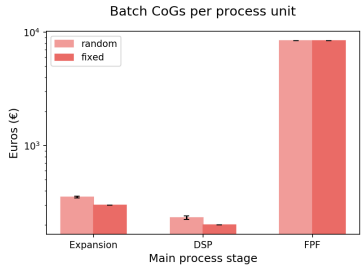

Figure 8: Batch CoGs per process unit (Expansion, DSP and FPF).

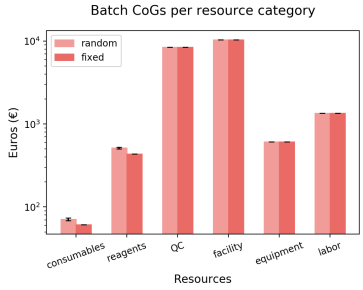

Figure 9: Batch CoGs per resource category (consumables, reagents, quality control, facility, equipment and labor).

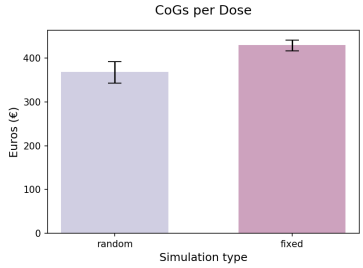

Figure 10: Direct and indirect CoGs per Dose.

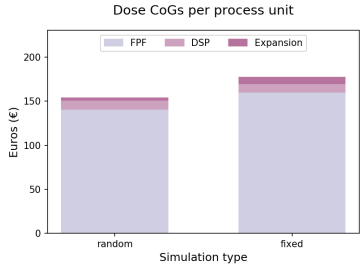

Figure 11: Dose CoGs per process unit (Expansion, DSP and FPF).

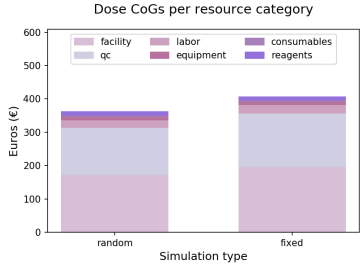

Figure 12: Dose CoGs per resource category (consumables, reagents, quality control, facility, equipment and labor).

and QC CoGs per Batch broken down into process units (Expansion, DSP and FPF - which corresponds to QC resource category). This means that for a simulation type the sum of its bars is equal to the sum of consumables, reagents and QC of Figure 9. In Figure 8, the Expansion and DSP bars in 'random' simulation type are larger than those corresponding to 'fixed' simulation type. Consequently, the bars for consumables and reagents - Figure 9 are also larger than the bars for the 'fixed' scenario. This is because in 'random' simulation type more cells have to be processed, spending more on the overall process (CoGs per Batch). Figure 10 shows the total CoGs per Dose for each simulation type 367.59€ and 429.35€ ('random' and 'fixed' respectively). This plot is analogous to the one in Figure 7, in the sense that to obtain it the CoGs per Batch are divided by the respective doses produced in that batch. Dose CoGs breakdown are presented either per process unit - Figure 11, or per resource category - Figure 12. The 'qc' and 'facility' parameters in Figure 12 are the main CoGs drivers (biggest ratio in comparison to the remaining categories) as it was seen in Figure 9. Because the objective is to obtain the lowest possible costs, these two categories might have room for improvement.

CUA

This section presents three levels of analysis: (i) CoGs per patient of the MSC-derived secretome, estimated from 'random' simulation type, remain the same (1,837.95€), and APS price is taken out of literature (690€) [11]; (ii) a reduction of 50% of CoGs per patient of the new therapy (from 1,837.95€ to 919€); and (iii) a reduction of 75% of CoGs per patient of the new therapy (from 1,837.95€ to 459.5€). The analysis was carried out by price clusters and three hypotheses were analysed: effectiveness of the new therapy same as APS, effectiveness of the new therapy 1.5 (0.6 QALY), and 2 times (0.8 QALY) higher than APS' effectiveness, respectively - Table 5.

Table 5: Incremental costs and incremental effectivenesses of MSC-derived secretome and APS therapies for three levels of analysis. CoGs per patient derived from 'random' simulation type were established as MSC-derived secretome price.

Price			Outcomes			
Secretome	APS	Δ Cost	Secretome	APS	Δ Effectiveness	**ICER**
1,837.95	690	1,147.95	0.4	0.4	0	0
1,837.95	690	1,147.95	0.6	0.4	0.2	5,739.75
1,837.95	690	1,147.95	0.8	0.4	0.4	2,869.9
919	690	229	0.4	0.4	0	0
919	690	229	0.6	0.4	0.2	1145
919	690	229	0.8	0.4	0.4	572.5
459.5	690	-230.5	0.4	0.4	0	0
459.5	690	-230.5	0.6	0.4	0.2	-1,152.5
459.5	690	-230.5	0.8	0.4	0.4	-576.3

In this study, it is assumed that the average

CoGs of therapy per patient is the price of the new therapy, because there is no information about this therapy regarding cost and effectiveness. On the other hand, the price of APS considered here is the cost of nSTRIDE APS kit, since is the only value available in literature [11].

The analysis hereby is presented in the last three rows of the Table 5.

Estimated Costs - Reduction of 75%

MSC-derived secretome price is estimated to be 1,837.95€, and a reduction of 75% makes up a total of 459.5€ - Expression 2. The IC would then be calculated - Expression 3.

$$1,837.95 \times 0.25 = 459.5 \tag{2}$$

$$IC = 459.5 - 690 = -230.5 \tag{3}$$

Equal Effectiveness In this scenario is considered that effectiveness in QALYs of MSC-derived secretome therapy is equal to APS (both 0.4 QALY) - first row of Table 5.

Kon et al. [16] report that utility of a OA patient, without any treatment, is 0.402 (man) and 0.394 (woman). Cumulative effectiveness was estimated, for a sample of patients with average age of 57, during 3 years of follow-up and according to Table 6, at a value of 0.293 (man) and of 0.292 (woman) QALYs.

Table 6: WOMAC scores converted in EQ-5D utilities and QALYs. Derived from [16].

WOMAC scores				EQ-5D utilities			QALYs	
Year	Pain	Stiffness	Function	Man	Woman	Time	Man	Woman
0	11.5	4.8	34.9	0.402	0.394			
1	4.3	2.7	15.6	0.735	0.727	0-1 year	0.333	0.333
2	4.5	2.4	14.4	0.74	0.732	1-2 year	0.005	0.005
3	5.7	2.8	18	0.695	0.686	2-3 year	-0.045	-0.046

van Drumpt et al. [18] point out that an OA patient without treatment at 57.5 years of age, QALY is estimated to be at 0.35 (man) and 0.34 (woman) - the baseline utility. The resulting gained QALY was estimated at 0.4 (for man and woman) - Table 7.

In this scenario, it is considered that effectiveness in QALYs of MSC-derived secretome therapy is equal to APS (both 0.4 QALY) - seventh row of Table 5. Once again, since the effectiveness of APS and MSC-derived secretome therapy is the same, a comparison can only be made in terms of costs. With the 75% reduction MSC therapy becomes more affordable (459.5€) than APS (690€).

Effectiveness of 1.5-fold A possible strategy for the new therapy to compete with APS would be to increase therapeutic outcomes allied to a cost reduction. It is established a scenario where the effectiveness of MSC-derived secretome is 1.5 times higher than APS, (0.6 QALY and 0.4 QALY, respectively), considering a price reduction of 75% - eighth row of Table 5.

Table 7: Extrapolation of WOMAC scores converted in EQ-5D utilities and QALYs. Derived from [18].

WOMAC scores				EQ-5D utilities	
Week	Pain	Stiffness	Function	Man	Woman
0	12	4.9	38.1	0.35	0.34
2	6.3	3.1	21.9	0.66	0.65
4	4.3	2.5	17.5	0.72	0.71
6	3.975	2.3	15.625	0.74	0.73
8	3.65	2.1	13.75	0.76	0.76
10	3.325	1.9	11.875	0.79	0.78
12	3	1.7	10	0.81	0.81
14	3.014	1.782	10.328	0.81	0.80
16	3.028	1.868	10.657	0.81	0.80
18	3.043	1.953	10.985	0.80	0.80
20	3.057	2.039	11.314	0.80	0.79
22	3.071	2.125	11.642	0.80	0.79
24	3.085	2.211	11.971	0.80	0.79
26	3.1	2.3	12.3	0.79	0.79
28	3.114	2.382	12.628	0.79	0.78
30	3.128	2.468	12.957	0.79	0.78
32	3.143	2.553	13.285	0.78	0.78
34	3.157	2.639	13.614	0.78	0.77
36	3.171	2.725	13.942	0.78	0.77
38	3.185	2.811	14.271	0.78	0.77
40	3.2	2.896	14.6	0.77	0.76
42	3.214	2.982	14.928	0.77	0.76
44	3.228	3.068	15.257	0.77	0.76
46	3.243	3.153	15.585	0.76	0.75
48	3.257	3.239	15.914	0.76	0.75
50	3.271	3.325	16.242	0.76	0.75
52	3.285	3.411	16.571	0.75	0.74

ICER is calculated, taking the previously IC value - Expression 3, and dividing it by the incremental effectiveness.

$$ICER = \frac{459.5 - 690}{0.6 - 0.4} = -1,152.5 \tag{4}$$

For this scenario ICER is -1,152.5€/QALY according to Expression 4. So, 1,152.5€ could express the saving for each QALY gained.

Effectiveness of 2-fold A scenario where the effectiveness of MSC-derived secretome is 2 times higher than APS, (0.8 QALY and 0.4 QALY, respectively), is also assumed while a price reduction of 75% is considered - ninth row of Table 5.

$$ICER = \frac{459.5 - 690}{0.8 - 0.4} = -576.3 \tag{5}$$

For this scenario, ICER is -576.3€/QALY which could mean that the implementation of the novel therapy represents a saving of 576.3€ for every each QALY gained - Expression 5.

Either for (i) 5,739.8€/QALY and 2,869.9€/QALY or for (ii) 1145€/QALY and 572.5€/QALY, the incremental cost and effectiveness are both positive - Figure 13. Therefore, MSC-derived secretome therapy is plotted in the NE quadrant. To interpret the results obtained, ICER needs to be compared with a specified threshold - WTP. Except when the effectiveness of the two therapies (MSC-derived secretome and APS) is equal, the novel therapy is cost-effective because it lies below the WTP.

Negative ICERs were calculated at values of (iii) -1,152.5€/QALY or - 576.3€/QALY, respectively for 1.5-fold or doubled the effectiveness scenarios - Figure 13. The negative ICER is associated to additional effectiveness, with the values for the novel therapy falling on the SE quadrant of the Figure 13, and this being more cost effective than the current treatment (APS), since interventions in this quadrant are less expensive and more effective.

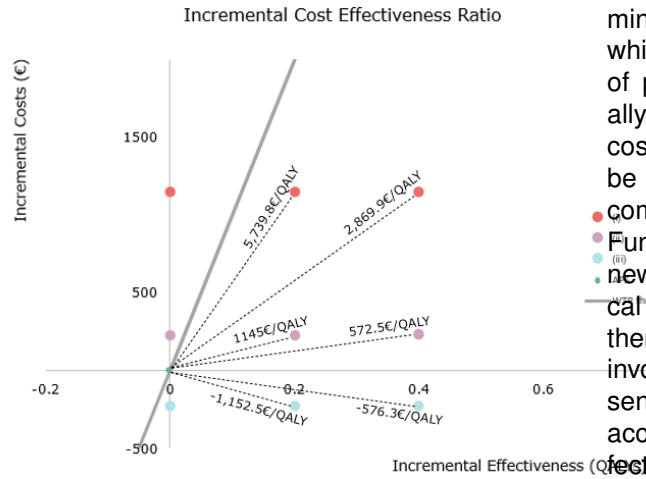

Figure 13: Cost-effectiveness plane with incremental effectiveness in QALYs on the x-axis and incremental costs in EUR on the y-axis. (i) corresponds to the first level; (ii) - second level and (iii) - third level of analysis.

In Figure 13, (i), (ii), and (iii) points represent the MSC-derived secretome therapy. Points on the y-axis represent the scenarios where the effectiveness of MSC-derived secretome is equal to the APS. Dashed lines connecting MSC-derived secretome therapy to the origin (APS therapy) represent the ICERs for each scenario. In this study, is established a WTP of 10,000€/QALY as reported in [25].

MCDA

MCDA aims to survey other aspects (patient lost wages, ease of therapy administration, etc.), important to be considered at the time of decision, which are not fully captured by CUA. Namely, it is important to consider not only the the impact for the patient but also for impact for the manufacturer and the health system administrator. In this way, MCDA is used as a reminder of the eHTA associated uncertainty and is then adopted in such a way as to contemplate variables (not exclusively related to the OA patients) that the previous analyses do not offer.

In addition to the manufacturing costs per patient of MSC-derived secretome and the patient outcomes measured in QALYs, other potential aspects should also be considered in order to have a broader view of the study, i.e. following a societal perspective. The incremental costs, incremental effectiveness, and ICER were calculated allowing to compare the new therapy against the comparator therapy. In this Section is investigated the socioeconomic impact of OA, highlighting that decisions are not limited to manufacturing costs alone: a cost only counts as 20% of the total cost per OA patient [19]. Direct costs of healthcare use in OA context (e.g. treatment acquisition and administration in patients), as well as indirect costs, which are not related to healthcare (e.g. lost wages of patients who suffer from OA) [26]. Additionally to those costs, administration and monitoring costs incurred by healthcare providers should also be covered in MCDA model. Apart from the outcomes studied only for the patient (Pain release, Function increase and Stiffness improvement), the new therapy can also bring benefits to the medical personnel, since the MSC-derived secretome therapy could be easy to administer and does not involve invasive procedures. In the value tree presented, the patient's risks are, among others, also accounted - it is crucial to take into account side effects when adopting a novel health therapy. Health risks can include both individual and public health risks affecting the wider population. Hence, the assessment of patient risks - health side-effects of the new ATMP should cover both short-term and long-term physical and psychological aspects [27].

A reminder should also be made regarding the factors inherent to the company, which will produce the therapy. As it seeks to receive the reimbursement of the product it will also be adopted a societal evaluation perspective. As one would expect, at this level of evaluation the company that will produce the new MSC-derived secretome must also take into account costs, benefits, risks and also usability as relevant aspects that are present in the initial stage of preparation of this MCDA tool in order to assist decision making. The manufacturers' objective are to produce the therapy at the lowest possible cost for maximum effectiveness in the patient's health (which is assessed through the endpoints aforementioned). It is also presented a set of risks to which the company is subject throughout the biotherapeutic development process.

To sum up, the point here is to consider either costs, benefits or risks not only to patient itself but also to their families, manufacturers and society as a whole. Along with the CUA model, one of the targets of this exploratory study is achieved here - to create awareness of what it will take for the medicinal product to be adopted or not.

5. Conclusions

This investigation include the estimation of the cost associated with an envisaged consisted in a study of the development of a manufacturing process for the production of an ATMP for the treatment of OA. The product was obtained after from the expansion of MSC from bone marrow, of allogeneic origin, in 2D system and downstream and purification of secretome/exosome produced by such cells. The process is operated according to GMP standards, ensuring the appropriate quality for its clinical application. The process Aiming aims at to treating of 200 patients per approximately a year, where each patient receives about five doses of the product, each dose containing $6.67x10^7$ exosomes. To reach this objective, it was concluded that it is necessary to perform approximately 18 or 21 batches ('random' or 'fixed' respectively). This corresponds to about 13 or 12 patients treated per successful batch produced. In order to treat a steady number of patients, surplus doses are discarded (42 and 8 doses, respectively for 'random' and 'fixed' simulation types). When information is available in the literature about the effectiveness of this therapy regarding patients' quality of life, and also about its costs, it will be possible to reduce the level of uncertainty presented throughout this exploratory study - eHTA. One will be able to consult this study and understand which should be the key drivers - e.g. patient costs, healthcare provider costs, clinical benefits, risks, that were involved in MCDA mapping. In the future, when the maturation of this preliminary model is completed, it will allow to support decisions on whether to adopt a new MSC-derived secretome, the specific target CoGs, and clinical endpoints that need to be reached to ensure cost-effectiveness competitiveness of the new therapy. Furthermore, this thesis points out the way forward until a final decision is reached. Within the approaches established in this work, it is clear that the adoption of the new OA therapies could save money and time resources, since *a priori* key features for the commitment of the entities to decision making have been revealed. This will help to speed up the decision making process, which in turn may lead to a high standard of care for OA patients.

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