A Bayesian Cost-effectiveness analysis of Holobalance, Holograms for personalized virtual coaching and motivation in an ageing population with balance disorders

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21 August 2021

A BAYESIAN COST-EFFECTIVENESS ANALYSIS OF HOLOBALANCE, HOLOGRAMS FOR PERSONALIZED VIRTUAL COACHING AND MOTIVATION IN AN AGEING POPULATION WITH BALANCE DISORDERS

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Abstract

Introduction: The world population is aging and it is only expected to grow in the next 30 years reaching 16% of the total world population (1). Globally, fall among older adults is a major public health problem.The burden of mortality and morbidity as a result of fall incidents is high in the elderly. There is a multitude of fall prevention programs designed based on the different risk factors associated with fall risk. Among these exercise programs have been shown to reduce the incidence of falls by 13% (6) to 40% (7).The Otago Exercise Program is an eight-week exercise that involves 17 different exercises that vary based on intensity with different repetitions and weight. It has been used as the cornerstone of most fall prevention exercise programs and has been shown to reduce fall risk in the elderly population by 35% (2,3). More recently, the use of virtual technologies has been an emerging phenomenon in the practice of elderly rehabilitation and exercise program. The Holobalance program, a novel methodology developed under the EU Horizon 2020 innovation project (8), was initiated to develop and validate a new personalized hologram coach platform for virtual coaching, motivation, and empowerment of the aging population with balance disorders.

Methods: Bayesian cost-effectiveness analysis of two alternatives namely Otago Exercise Program and Holobalance technology is performed by considering the relevant probabilities of the outcomes, the associated cost, and utility loss for each relevant outcome for three countries i.e. Italy, Germany, and Greece. Relevant data was obtained using literature review of the enumerated parameters and the associated cost as well as utility. Additional data regarding Holobalance technology was obtained from the first data of an ongoing clinical pilot.

Results: The ICER associated with the highest WTP under consideration, 30000€, is - 103879 for Italy, -86560 for Greece, and -107666 for Germany. The average expected utility loss for the WTP of 30,000 Euros in the case of the Otago exercise program is -819.51, -624.77, -774.41 for Italy, Greece, and Germany respectively. In the case of Holobalance, it is -478.31, -352.57, and -383.53 respectively for Italy, Greece, and Germany. All the values of the EIB are positive in all of the willingness to pay values that were considered (10,000, 25,000, 30,000) for all of the three countries. The mean cost for to implement Otago exercise program is higher compared to the average cost for Holobalance for the three countries.

Conclusion: In all the three countries considered in this analysis, Holobalance is found to be more cost-effective than the Otago exercise program. In this Bayesian Cost-Effectiveness Analysis, the Holobalnce technology is the dominant alternative with a lower cost and a higher level of effectiveness compared to the current standard therapy i.e Otago Exercise program.

Keywords: Bayesian Cost Effectiveness Analysis, Holobalance, Fall, Elderly, Virtual Reality, Economic Evaluation

Background

The world population is aging and it is only expected to grow in the next 30 years reaching 16% of the total world population (1). Increased life expectancy and decreased fertility rate are significantly contributing to the growing proportion of the aging population. As a result, diseases and disorders that are commonly seen in older individuals are becoming increasingly common. Among these, osteoporosis results in loss of bone and muscle mass that restricts mobilization which together with the cognitive decline and coordination result in falls and fragility fractures. Fall in the elderly is a result of an interplay between many risk factors that end up with a vicious cycle of immobilization and fragility.

Globally, fall among older adults is a major public health problem. Reports signify that, from 25% (CDC,2021) to 33% (2,3) of older individuals above the age of 65 fall each year. The burden of mortality and morbidity as a result of fall incidents is high in the elderly. Although a major share (80%) (4) of falls result either in no or minor injuries, fractures mainly that of hip and head injuries are serious consequences with associated mortality, lost quality of life, long-stay care costs, and hospital inpatient costs. In the 2018 more 85% hospital discharges by fracture of femur and the 86% of total causes of death for fall are individuals 65 years and over in EU 27(EUROSTAT). Around 25 billion euros are spent treating fall-related injuries across the EU every year and this number is projected to reach 45 billion Euros by the year 2050.[5]

There is a multitude of fall prevention programs designed based on the different risk factors associated with fall risk. These programs include exercise, nutritional therapy such as Calcium and Vitamin D supplementation, environmental modifications, cognitive-behavioral therapies, vision assessment and treatment, medication review and modification as well as assistive technologies for communication and signaling during a fall. Among these exercise programs have been shown to reduce the incidence of falls by 13% (6) to 40% (7). Among the most commonly applied exercise-based fall prevention schemes are the Otago Exercise Program (OEP), TaiChi, and Falls Management Exercise intervention (FAME). Multifactorial interventions that assess individual risks and adapt to the identified factors have shown better results using one or more of these interventions.

Among these, the Otago Exercise Program is an eight-week exercise that involves 17 different exercises that vary based on intensity with different repetitions and weight. It has been used as the cornerstone of most fall prevention exercise programs and has been shown to reduce fall risk in the elderly population by 35% (2,3). In order to increase the accessibility of exercise programs especially to those who are homebound, different modalities and technologies have been developed. More recently, the use of virtual technologies has been an emerging phenomenon in the practice of elderly rehabilitation and exercise program.

Virtual reality tools create a three-dimensional interactive environment that mimics reality thus lifting the barrier in the implementation and acceptability of exercise programs. In addition, these tools can be used from remote creating an additional comfort and sense of autonomy among individuals. The Holobalance program, a novel methodology developed by consortium of 13 partners (University of Ioannina, University College London , University Medical Center Freiburg Neurocenter, Bioirc, National and Kapodistrian University of Athens, Institute of Communication and Computer Systems, Kings College London, University of Hamburg, Age Concern London, Sphynx Technology Solutions, Eipix Entertainment, Roesssingh Research and Development, Quantitas) under the EU Horizon 2020 innovation project (8), was initiated to develop and validate a new personalized hologram coach platform for virtual coaching, motivation, and empowerment of the aging population with balance disorders. Holobalance is designed to provide a telerehabilitation system that will provide an individualized and regularly reviewed program by a specialist balance physiotherapist to participants in the home environment. The telerehabilitation system will attempt to increase user motivation through augmented reality gamification of the exercises. The system provides a surrogate physiotherapist provided by means of a hologram that provides real-time feedback to motivate the individual.

A cost-effectiveness analysis of the Holobalance study is conducted to evaluate the incremental effect that this technology will provide considering the investment needed. Since it is a novel technology undergoing a pre-trial phase, a large volume of data is not available to materialize the analysis. As such, modeling strategies were used. In this study, a Bayesian perspective was used to implement the cost-effectiveness analysis, and a Markov Chain Monte Carlo (MCMC) method was used to obtain the simulation of the relevant input priors and derived values, to be integrated into the model to evaluate the cost-effectiveness of Holobalance compared to the Otago exercise program. This analysis is performed for Germany, Italy, and Greece using data available for these countries.

Methods

Data and assumptions

To compare the expected costs and consequences of decision options, information on the different parameters was collected from literature, scientific articles, and expert opinions. The approach is a decision-analytic model and a decision tree is used to outline fall-related events and their related consequences (cost and utility). Holobalance coach platform is the intervention of interest and the Otago exercise program is used as a comparator.

This analysis is performed for Italy, Greece, and Germany, and the time span considered for the probabilities, the costs, as well as the loss of utility, is a duration of one year. The target population in this analysis is elderly individuals from 65-80 years of age who sustained at least one fall in the past year. Accordingly, a decision tree was built considering the common service levels and common outcomes that are relevant for elderly fall. The relevant outcomes that are considered in the analysis are the ones in the decision tree.

In figure 1 the decision tree is displayed and it is assumed that if an individual sustains a fall with a serious injury the individual might visit his/her General Practitioner or end up in the Emergency department (ED). Among those who visit the ED some individuals will be hospitalized which can be for a fracture or for another diagnosis. Since fracture is an important injury because of the associated sequel and costs of treatment, it was considered separately. Other injuries that are associated with an elderly fall are bundled under the term “other diagnosis” and inside individuals who suffered and were admitted for Head injury, Dislocations, Internal injury, Open wound, Contusion, and Sprain/strain were considered. After being hospitalized individuals can end up being discharged into their home (usual residence), transferred into a nursing home, or die.

For both the Otago exercise program and the Holobalance technology, the acceptance of the exercise program or the technology, the effectiveness in reducing falls, and the costs to implement these interventions were considered. The acceptance of the Otago exercise program (which was expressed as the adherence to the exercise by individuals) was taken from literature. The effectiveness(which is the percentage of reduction in fall with the exercise program), is described in different trials based on the results they have obtained. These values representing the effectiveness of Otago were weighted and averaged based on the sample size of the specific study from which they were taken in order to obtain the value of Otago effectiveness to be used for this analysis.

The acceptance of the Holobalance technology is expressed as digitalization - a weighted value of internet home access and digital skill of the elderly population. It was assumed that except for those elderly individuals with no overall digital skill the others will be able to use the Holobalance technology which can be a proxy to estimate the acceptance of Holobalance. The effectiveness(which is the percentage of reduction in fall with the Holobalance technology) is calculated from the values obtained in the pilot study for Holobalance technology in Germany by University Freiburg partner HB consortium. The sample size of the pilot was very small with a large Confidence Interval considering that it was obtained from one site and the duration of the pilot is 4 months. To obtain the effectiveness of Holobalance for the duration of one year the formula for calculating probability over a different time interval was used (9).

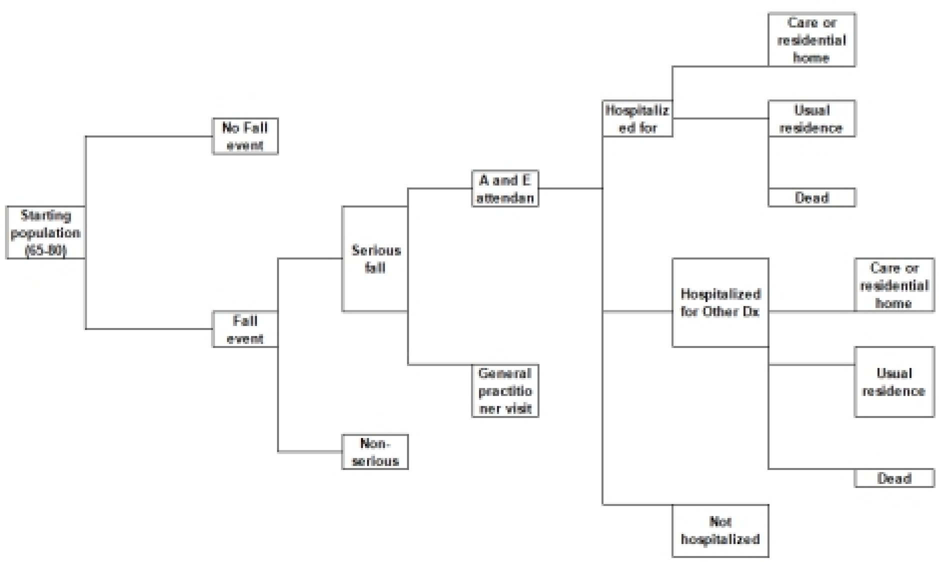

Figure 1: Decision tree

<u>Cost</u>

All relevant costs were expressed in Euro and country-specific costs were used based on the recently applicable DRGs (Diagnosis-related groups) for hospitalization and costs for subsequent care. The costs related to admission and inpatient stay are considered based on the average length of stay of the specific diagnosis except for transfer to a nursing home where the duration of one year was considered. For costs related to outpatient visits such as General Practitioner and Emergency Department visits, the national average cost per visit of each country was used. (see table 1)

The cost of the Otago exercise program for one year (expressed in euros) includes the material costs and the professional cost for the training calculated for one individual for the duration of one year. This information was also taken from different literature (57). The cost for the Holobalance technology was calculated for one year (expressed in euros) including the material costs(both software and hardware), professional cost (Physiotherapist) for initial assistance, and training calculated for one individual for the duration of one year (see table 2). The information regarding the hardware and the software costs are estimated according to the existing protocols for similar balance training exercises for elderly falls.[10]

<u>Utility</u>

The quality-adjusted life year (QALY) that is associated with the relevant outcomes is expressed in terms of a utility loss. Accordingly, the values representing the QALY loss were obtained from different literature that estimated the respective utility loss associated with the relevant outcomes. Health-related quality of life is measured on a scale of 0 (death) to 1 (perfect health) using a utility instrument (EQ-5D) which measures individual strength of preference between alternative health states. The EuroQol (EQ-5D-5L) is a valid and reliable instrument widely used to obtain utility weights and it has been used for fall-related conditions in older populations in different literature as well. These Utility weights were then taken and combined with time spent in different health states to calculate QALY. The QALY used in the analysis is the change in QALY over the time of one year after sustaining the respective outcomes. The utility weights used in the EQ-5D have been sourced from published results for similar populations except for the QALY associated with sustaining a serious injury where the average utility loss corresponding with common serious injuries was taken to represent the utility loss due to the absence of evidence from the literature [11].

Statistics for OTAGO and Holobalance							
	Parameter			Distribution	Mean	SD	Source
1	OTAGO effectiveness		ρ1	Lognormal	0.29	0.034	(61)
2	OTAGO acceptance(~adherence)		Φ2	Beta	0.53	0.19	(62),(63)
3	Digitalization	GERMANY	Φ1	Beta	0.941	0.01	Eurostat
		ITALY		Beta	0.816	0.083	Eurostat
		GREECE		Beta	0.782	0.083	Eurostat
4	Holobalance effectiveness		ρ2	Lognormal	0.508	0.322	Pilot Data

Table 1: Outcome values summary for Otago and Holobalance

Bayesian Cost-effectiveness analysis (BCEA)

A Bayesian model specifies a full probability distribution to describe uncertainty. By the basic rules of probability, it is always possible to factorize a joint distribution as the product of a marginal and a conditional distribution. Consequently,

$$p(y, \theta) = p(\theta)p(y|\theta) = p(y)p(\theta|y)$$

from which Bayes' Theorem follows in a straightforward way which is the base for the Bayesian method.

Any p() here is a probability density function (pdf) and is not a single probability value Where $p(\theta.y)$ implies the posterior pdf

$p(\theta)$ is the prior pdf for our parameter of interest

$p(y, \theta)$ is the pdf for the likelihood function

$p(y)$ is the pdf for available evidence,

The posterior probability defines a revised probability based on additional information where as the prior probability is the initial probability based on the initially available evidence.

Bayesian Statistical Model and Economic analysis are based on the following assumptions:

1. The population of individuals to be included in the study are those aged between 65-80 in each country (Italy, Greece, and Germany)
2. The number of individuals participating in the two reference technologies/interventions when available are described by a Binomial distribution which considers the acceptance of the two interventions.
3. The probability of fall and subsequent outcomes were considered for two groups of individuals using the Otago exercise program and the Holobalance technology. Due to the lack of directly measured information and the difficulty in finding the probabilities representing all of the outcomes used in the analysis for the three countries, a literature review was conducted to identify the relevant parameters. Then, a weighted average was taken initially using the sample size and then aggregated to be assimilated into the model using the population proportion of each country.
4. The relevant clinical outcomes compared are given in table 3.
5. The baseline probability of occurrence of fall was initially taken and a Beta distribution was assumed. Then the proportional reduction in the probability of fall, due to the use of the Otago exercise program and the Holobalance technology, was assumed as a multiplying factor of the baseline probability of occurrence.

6. The number of individuals who sustained at least one fall in each group is distributed as a binomial with parameters attached to each one of them (see table 3). By combining these probabilities with the relevant populations at risk we can derive the expected number of individuals experiencing each of these events for the three countries.

In the Bayesian cost-effectiveness analysis (BCEA), two alternatives namely Otago Exercise Program and Holobalance technology will be compared by considering the relevant probabilities of the outcomes, the associated cost, and utility loss for each relevant outcome for the three countries. It is considered that the two alternative exercise programs will be used up by the individuals when they are available based on their acceptance rate.

Material cost in Euro	
Yearly cost for one person	
Software	60
Hardware	141.6
Total	201.6
Physiotherapist training and supervision cost	168.77
Final HB Cost/person/year	370.375
SD HB cost/person/year	92.59375

Table 2: Holobalance cost

<u>Markov Chain Monte Carlo Sampling</u>

Each set of variables listed in Table 3 will have an associated probability density function. The idea is to combine all these distributions together with the MCMC strategy to get an estimate of the posterior distribution for costs and effectiveness. From here we can obtain the average cost for the population. The main simulation method for Bayesian inference is Markov Chain Monte Carlo (MCMC) that is used to construct a Markov chain, a sequence of random variables for which the distribution of the next value only depends on the current one, rather than the entire history. This process can be repeated until convergence is reached after which it is possible to use the simulated values to compute summary statistics (e.g. mean, standard deviation or quantiles).

Subsequently, the economic model that represents the utility associated with a certain health intervention with a cost of c and effectiveness of e will be:

$$Ut = Ke_t - c_t$$

where Ut represents the average expected monetary loss under the interventions considered, K is the willingness to pay and ct is the expected average population cost for the intervention and et represents the QALY gained/lost as a result of the intervention. [64]

The process starts with a statistical model that is used to estimate some relevant parameters, which are then fed to an economic model with the objective of obtaining the relevant population summaries indicating the incremental benefits and costs for a given intervention. These are in turn used as the basis for the decision analysis. The final aspect is represented by the evaluation of how the uncertainty that characteristics the model impacts the final decision-making process.

In line with the precepts of (Bayesian) decision theory, given current evidence, the “best” intervention will be the one associated with the maximum expected utility. This is because it can be easily proved that maximizing the expected utility is equivalent to maximizing the probability of obtaining the outcome associated with the highest (subjective) value for the decision-maker.

Values table for the whole data set

								GERMANY		ITALY		GREECE		
	Outcomes													
		Sign	**Distribution**		**Weighted mean for 65-75**	**Weighted mean for >75**	**Source**	**Population weighted mean**	**SD**	**Population weighted mean**	**SD**	**Weighted mean**	**SD**	**Description**
1	Fall	β1	Beta		0.2364	0.2925	[17]	0.2532	0.0724	0.2521	0.0721	0.2510	0.0718	The risk/ probability of falling
2	Serious inj	β2	Beta		0.2098	0.2527	[18][19][20][21]	0.2227	0.0629	0.2218	0.0621	0.2210	0.0613	The risk/probability of suffering serious injury(those requiring medical attention) among those who fall
3	Non seriou	β3	Beta		0.7902	0.7473	[18][19][20][21]	0.7773	0.0629	0.7782	0.0621	0.7790	0.0613	The risk/probability of not suffering serious injury(those not requiring medical attention) among those who fall
4	GP	β4	Beta		0.2052	0.1617	[22][23]	0.1921	0.2749	0.1930	0.2749	0.1939	0.2749	The probability of visiting a Gp after serious injury from fall incident
5	ED	β5	Beta		0.7948	0.8383	[22][23][24][25]	0.8079	0.2749	0.8070	0.2749	0.8061	0.2749	The probability of visiting the Emergency after serious injury from fall incident
6	FRX.hosp	B6	Beta		0.1627	0.1979	[26][27][28][29][30][31][32][33]	0.1732	0.0662	0.1725	0.0663	0.1718	0.0663	The probability of being admitted with the diagnosis of Fracture among those who visited the Emergency for serious injury from fall incident
7	OtherDx.h	β7	Beta		0.1473	0.1979	[26][27][28][29][30][31][32][33]	0.1625	0.0402	0.1614	0.0400	0.1604	0.0397	The probability of being admitted with the non-fracture related diagnosis among those who visited the Emergency for serious injury from fall incident
8	Non.Hosp	β8	Beta		0.6901	0.6042	[26][27][28][29][30][31][32][33]	0.6643	0.1517	0.6660	0.1514	0.6677	0.1512	The probability of not being hospitalized am
9	D.home.FI	β9	Beta		0.4222	0.4222	[34][35][36][37][38]	0.4222	0.2352	0.4222	0.2352	0.4222	0.2352	The probability of being discharged to home after hospital admission for the diagnosis of fracture
10	Death.FRX	β10	Beta		0.0545	0.0545	[34][35][36][37][38]	0.0545	0.0369	0.0545	0.0369	0.0545	0.0369	The probability of death after hospital admission for the diagnosis of fracture
11	NH.FRX	β11	Beta		0.1455	0.1455	[26][27][28][29][30][31][32][33][34][35][36] [37][38]	0.1455	0.2381	0.1455	0.2381	0.1455	0.2381	The probability of benig transfered to nursin
12	D.home.ot	β12	Beta		0.8728	0.8679	[39][40][41][42][43]	0.8714	0.2178	0.8715	0.2179	0.8715	0.2179	The probability of being discharged to home
13	Death.othe	β13	Beta		**0.0306**	**0.0355**	[41] [42][43]	0.0321	0.0163	0.0320	0.0165	0.0319	0.0167	The probability of death after hospital admission for non-fracture related diagnosis
14	NH.otherD	β14	Beta		0.0966	0.0966	[39][40]	0.0966	0.0241	0.0966	0.0241	0.0966	0.0241	The probability of benig transfered to nursing care facility after hospital admission for non-fracture related diagnosis

	Costs(resources)													
							Source	**Population weighted mean**	**SD**	**Population weighted mean**	**SD**	**Weighted mean**	**SD**	**Description**
1	General Practitioner's visit cost (GpC)	Ψ1	Gamma				[44][45][46]	17.6200	1.4400	14.4200	3.6050	14.0000	5.0000	Cost per visit
2	Emergency visit cost (EvC))	Ψ2	Gamma				[47][48][49]	200.89	50.22	25.00	6.25	50.00	12.50	Cost per visit
3	Inpatient admission cost for fracture (INpC)	Ψ3	Gamma				[50][51][52][53]	6694.236	2177.447	2250.600	1380.547	967.5500	949.9870	Cost per admission for average LOS
4	Inpatient admission cost for other Dx(INpC)	Ψ4	Gamma				[54][55][56]	20.4040	1262.650	5967.450	4721.216	655.9500	320.3215	Cost per admission for average LOS
5	OTAGO cost (OTA_C)	Ψ5	Gamma				[57]	419.5200	135.8300	419.5200	135.8300	419.5200	135.8300	Intervention cost per single participant
6	HOLOBalance cost (HB_C)	Ψ6	Gamma					370.0000	92.6000	370.0000	92.6000	370.0000	92.6000	Intervention cost per single participant
7	Nursing care facility cost (NFC	Ψ7	Gamma				[58][59]	34675	8669	41099	10275	13140	3285	Cost per admission for average LOS

	QALY												
						Source	Population weighted mean	SD	Population weighted mean	SD	Weighted mean	SD	Description
1	Fall (FQly	ω1	Beta			[60]	0.0200	0.004	0.0200	0.0040	0.0200	0.0040	QALY of a person for one year after a fall incident (based on utility values)
2	Suffering s	ω2	Beta			[60]	0.0600	0.0523	0.0600	0.0523	0.0600	0.0523	QALY of a person for one year after suffering serious injury from fall incident (based on utility values)
3	Emergenc	ω3	Beta			[60]	0.0300	0.0295	0.0300	0.0295	0.0300	0.0295	QALY of a person for one year after visiting the emergency for suffering serious injury from fall incident (based on utility values)
4	Fracture r	ω4	Beta			[60]	0.0700	0.0538	0.0700	0.0538	0.0700	0.0538	QALY of a person for one year after being admitted to the hospital for the diagnosis of fracture after a fall incident(based on utility values)
5	Non-fractu	ω5	Beta			[60]	0.0400	0.0112	0.0400	0.0112	0.0400	0.0112	QALY of a person for one year after being admitted to the hospital for the non-fracure related diagnosis after a fall incident(based on utility values)
6	Nursing ca	ω6	Beta			[60]	0.0700	0.0675	0.0700	0.0675	0.0700	0.0675	QALY of a person for one year after being admitted to a nursing care facility after hospital admission for a fall incident(based on utility values)

Table 3: Summary of the parameter values for outcomes, cost and QALY considered for the Bayesian Cost Effectiveness Analysis

Results

The MCMC summary

The MCMC summary table shows us information about the relevant parameters for the simulated posterior distributions through MCMC, like the mean, standard deviation, and percentiles for the outcome parameters, the costs, and the QALY's assumed in the analysis. A detailed summary of the MCMC table can be seen in figure 1. (see appendix)

Cost-effectiveness decision parameters

The consequences of each intervention will be expressed in terms of a utility function as a net monetary benefit which takes into account the average monetary loss under interventions 1 and 2. Subsequently, the intervention associated with a lower average loss of utility is preferred. In this case, the analysis was performed for the willingness to pay values of 10000€, 25000€, and 30000€ in order to be able to compare the change in the ICER.

WTP	Parameter	Italy		Optimal intervention	Germany		Optimal intervention	Greece		Optimal intervention
		HB	OEP		HB	OEP		HB	OEP	
WTP= 10000	Utility	-318.37	-608.6	HB	-227.04	-561.13	HB	-187.89	-413.39	HB
	EIB	290.23			334.1			225.5		
	CEAC	1			1			1		
	ICER	-103879			-107666			-86560		
	EVPI	1.06E-14			-4.59E-15			-5.93E-15		
WTP= 25000	Utility	-438.33	-766.78	HB	-344.4	-721.09	HB	-311.4	-571.93	HB
	EIB	328.45			376.69			260.53		
	CEAC	1			1			1		
	ICER	-103879			-107666			-86560		
	EVPI	-6.127E-15			-2.46E-15			-1.566E-		

								15		
WTP= 30000	Utility	-478.31	-819.51	HB	-383.53	-774.41	HB	-352.57	-624.77	HB
	EIB	341.2			390.88			272.2		
	CEAC	1			1			1		
	ICER	-103879			-107666			-86560		
	EVPI	1.13E-14			-2.38E-14			0.035		

Table 4: Summary of CE- decision parameters and PSA parameter values for Italy, Germany and Greece

Looking at the results from the summary table 4 we can see that intervention 2 which is the Holobalance technology is the cost-effective alternative compared to the Otago exercise program for all of the willingness to pay values that were considered in the analysis. From the results in the summary table 4, we can also see that all of the expected utility values are negative in all of the willingness to pay values for Italy, Greece, and Germany. Considering that we are using the net monetary benefit as our utility function, this is due to the associated QALY loss by sustaining a fall and this will translate into a monetary loss. The average expected utility loss for the WTP of 30,000 Euros in the case of the Otago exercise program is -819.51, -624.77, -774.41 for Italy, Greece, and Germany respectively. In the case of Holobalance, it is -478.31, -352.57, and -383.53 respectively for Italy, Greece, and Germany.

The ICER associated with the highest willingness to pay under consideration, 30000€, is -103879 for Italy, -86560 for Greece, and -107666 for Germany. Considering that the ICER is negative it could be in the second or the fourth quadrant in the cost-effectiveness plane indicating that the intervention of interest is completely dominant or dominated therefore we have to consider other parameters like Expected Incremental Benefit and Cost-Effectiveness Acceptability Curve.

The Expected Incremental Benefit (EIB)

The EIB tells us the expected average incremental benefit by computing the average incremental benefit of each simulation (the difference between the expected utilities of the two alternatives). For the intervention of interest to be cost-effective the EIB should be greater than 0, taking the WTP into account.

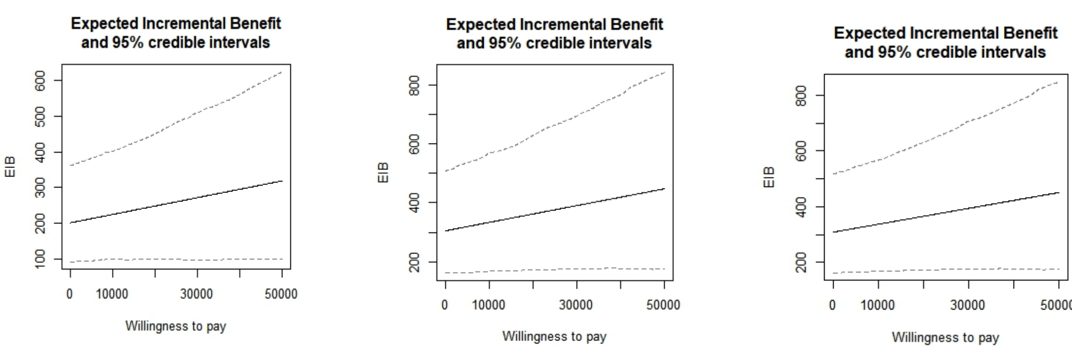

Figure 2: Expected Incremental Benefit (EIB) for Italy, Greece and Germany respectively

The individual incremental benefits of the specific simulations can be seen in the BCEA output. All the values of the EIB are positive in all of the willingness to pay values that were considered (10,000, 25,000, 30,000) for all of the three countries. We can also see that the value of the EIB increases as the willingness to pay increases. The expected incremental benefit (EIB) for the willingness to pay of 30000 is 341.2 for Italy, 272.2 for Greece and 390.88 for Germany therefore Germany has the highest EIB, and Greece has the lowest.

The Cost-Effectiveness Plane (CE- Plane)

The CE- Plane shows simulations from the joint (posterior) distribution of the random variables. The CE plane is used to visualize heterogeneity of the simulations by comparing the differential gains in QALY and cost from the two interventions, also weighting the average. In addition, a contour plot further shows us that from 94.4% - 97.6% of the simulated points lie in the fourth quadrant of the cost effectiveness plane which is the dominant quadrant for the three countries.

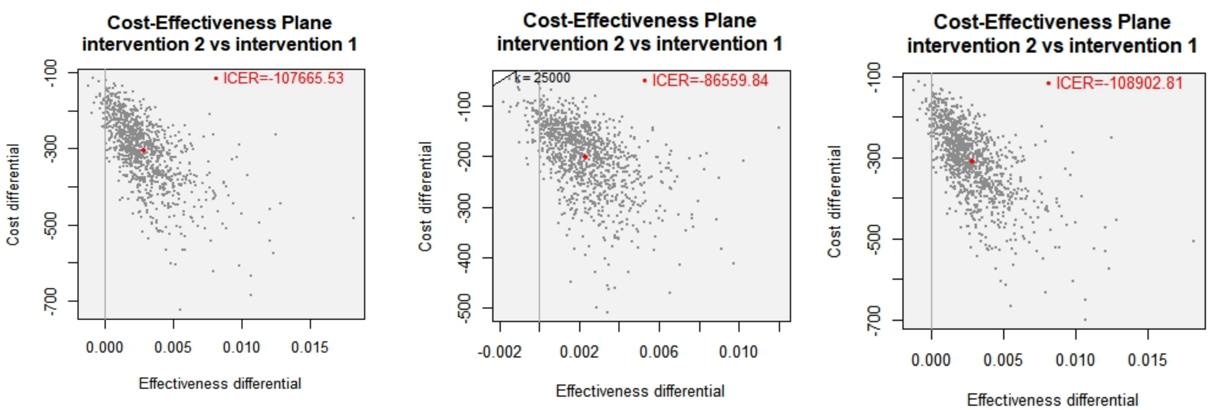

Figure 3: Cost Effectiveness plane for Italy, Germany and Greece

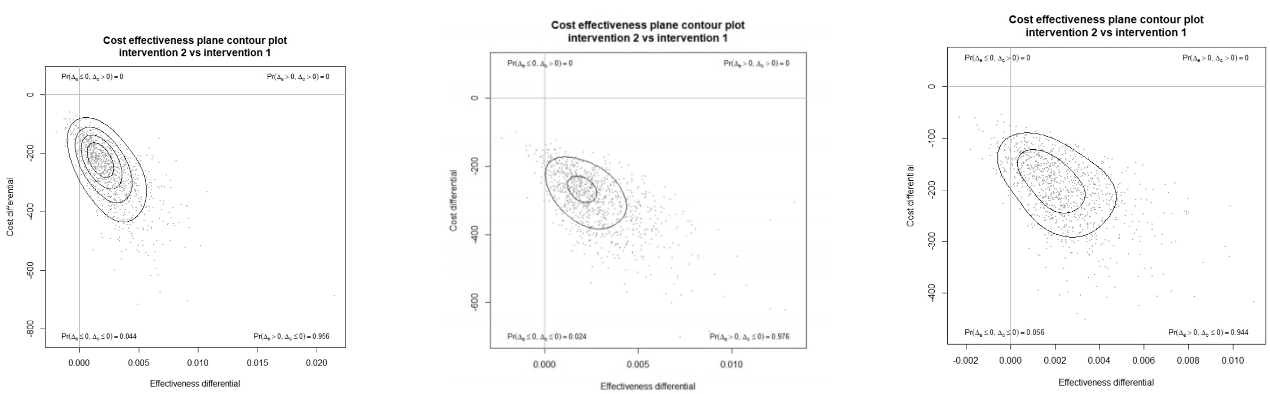

Figure 4: Contour plot for Italy, Germany and Greece

Probabilistic Sensitivity Analysis (PSA)

Probabilistic Sensitivity Analysis is a technique used in economic modeling that helps quantify the level of confidence in the output of the analysis in relation to the uncertainty of the model inputs. Parameters such as CEAC and EVPI will tell us the degree of uncertainty involved in the decision regarding the outputs of the analysis. [12]

<u>Cost-Effectiveness Acceptability Curve (CEAC)</u>

The CEAC estimates the probability of cost-effectiveness for different WTP thresholds. It is used to evaluate the uncertainty with the decision-making process by quantifying the degree to which a certain intervention is preferred compared to the alternative intervention. We can see from the summary table 8 that in the case of this analysis the CEAC is 1 or 100 percent for all of the willingness to pay values for Italy and Germany as well as for Greece since the intervention of interest(Holobalance technology) is the cost-effective alternative for all of the willingness to pay values.

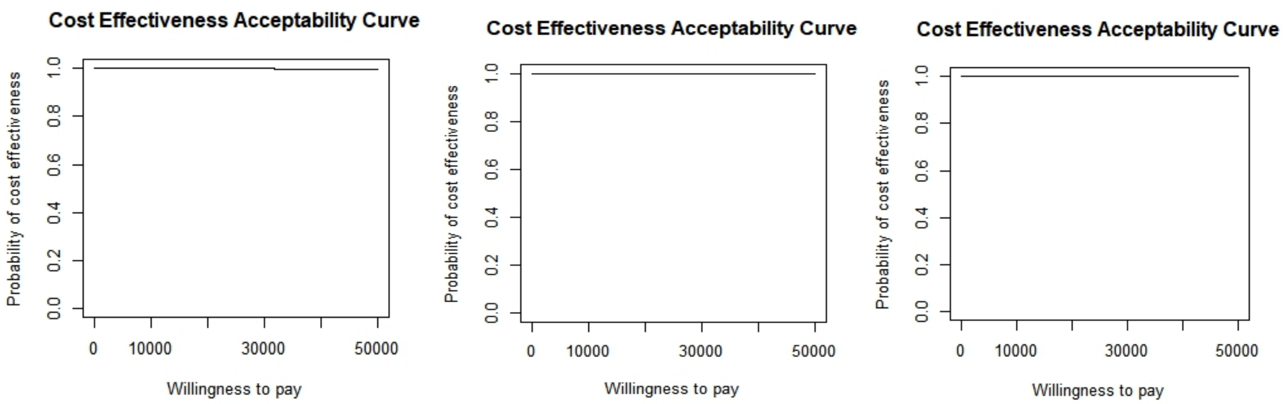

Figure 5: Cost Effectiveness Acceptability Curve for Italy, Germany and Greece

<u>Expected Value of Perfect Information (EVPI)</u>

Expected Value of Perfect Information (EVPI) is a measure to translate uncertainty associated with the cost-effectiveness evaluation in the model into an economic quantity. It is expressed with an Opportunity Loss (OL) in order to measure the potential losses caused by choosing the most cost-effective intervention on average when it does not result in the intervention with max utility in the future. We can see EVPI being reported at the very end of the summary table 8 and it is a very small (negligible) value and even negative in some of the cases for all of the willingness to pay values used for Italy, Greece, and Germany.

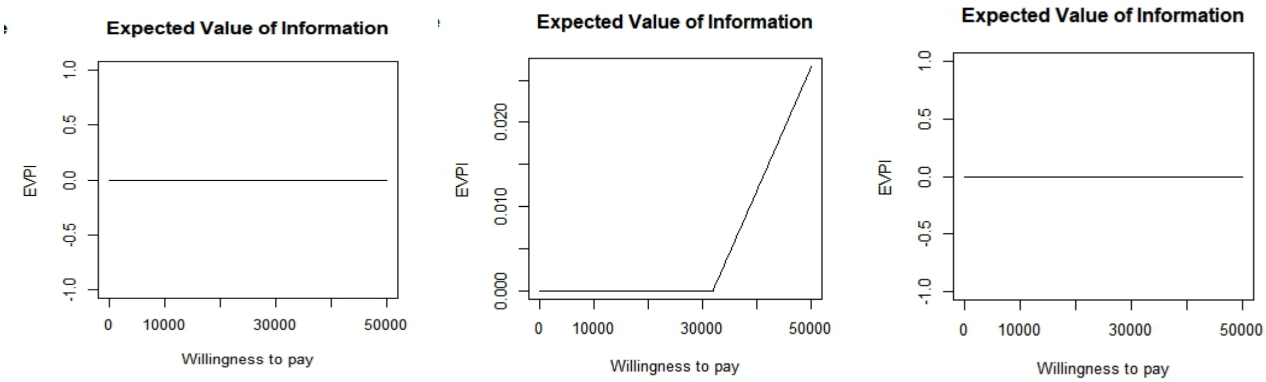

Figure 6: Expected Value of Information for Italy, Germany and Greece

Mean cost and effectiveness over the population considered

Table 5 shows the mean cost and effectiveness for Otago and Holobalance in the three countries. This tells us the mean per-person cost to implement the interventions and the associated effectiveness per individual. The mean cost for Otago is 503.1, 454.5, and 307.7 for Italy, Germany, and Greece which is higher compared to the average cost for Holobalance.

Parameter	**Italy**		**Germany**		**Greece**	
Intervention	HB	Otago	HB	Otago	HB	Otago
Mean cost	238.4	503.1	148.79	454.5	105.55	307.7
Mean Effectiveness (In QALY loss)	-0.007997	-0.010546	-0.007824	-0.010664	-0.008234	-0.010569

Table 5: Mean cost and Effectiveness for Otago Exercise program and Holobalance for Italy, Germany and Greece

Discussion

The main finding from this study is that implementing Holobalance as a personalized virtual coaching and motivation tool in an aging population with balance disorders not only is a cost-effective intervention but also a cost-saving option having higher effectiveness and a lower cost compared to the comparator studied, i.e Otago exercise program. There is no previous literature to represent the effectiveness of Holobalance due to its novelty but based on the value obtained from a clinical pilot with small sample size, the effective reduction of fall risk by Holobalance is higher than (51%) that of Otago (29%) over a one year period of consideration.

The increase in effectiveness can be attributed to the method of rehabilitation that is targeted by the technology. In addition, the adherence level in those individuals who are using the Holobalance technology is superior compared to Otago. Other factors like the motivation of the individuals in the continuous engagement have to be taken into account in achieving better results other than the frequency of the exercise. As a matter of fact, Holobalance uses user-friendly and off-the-shelf technologies which clinicians can prescribe to provide individualized balance rehabilitation sessions for older adults who can participate according to their time and place preference. (13) Moreover, individually tailored exercise programs taking personal factors and individual preferences into account, as well as increased supervision by professionals, are key aspects of the success of balance exercise programs like that of Holobalance to attain sustainable long-term results.

In this study, digitalization is used as a proxy for the adherence level of individuals using the Holobalance technology. This variable, which is an aggregate of the digital skill and internet access in each of the countries under consideration, ranges from 94.1% in Germany to 81.6% in Italy and 78.2% in Greece. This shows us that Germany has much higher digitalization coverage compared to the other two countries, which clearly increased the number of individuals that can potentially enroll to use this technology. In contrast, Italy has a lower rate of digitalization resulting in a smaller proportion of the population that is expected to utilize and benefit from Holobalance.

It has been a well-established fact that the probability of fall and the effectiveness of fall prevention programs depends on age. Regardless, Italy, Germany, and Greece have a very similar proportional composition of a population from 65-80 years of age signifying a limited impact of the difference in the age composition on the outcomes related to the cost-effectiveness of both Holobalance and Otago exercise program.

In all the three countries considered, Holobalance is found to be more cost-effective than the Otago exercise program using the Bayesian cost-effectiveness analysis methodology. This is also true in the three cases of willingness to pay values considered (10,000 Euro, 25,000 Euro, and 30,000 Euro). Considering the mean cost per intervention across the entire population from 65-80, Holobalance has a lower cost per person in all three countries. The cost of Holobalance for a year per person is 370 Euro which is lower than the cost of Otago (419.52 Euro). This reduction in the cost is mainly a result of decreased overhead costs for training sessions by physiotherapists. Evidence from other interventional and cost-effectiveness studies suggests that the average intervention cost for Otago is highly influenced by staff salary costs(14). Nearly 75% of the cost of Otago is consumed for labor and travel time costs according to studies (14) while this cost makes up 45.4% in the case of Holobalance technology.

There is an inter-country level difference in the cost to apply both interventions over the population. For Holobalance, It can be seen that in Italy, the mean cost per person is 238.4 Euro (Vs 503.1 for OEP), the highest among the three countries followed by Germany which is 148.79 Euro per person (Vs 454.5 for OEP) and lastly Greece which is 105.55 Euro per person (Vs 307.7 for OEP). Looking at the mean loss in the quality of life in the three countries indicates that Holobalance results in a lower loss in quality of life compared to Otago. This loss is slightly higher for Greece compared to Italy and Germany. It has been reported in randomized clinical trials (RCTs) that individuals using virtual technologies for rehabilitation have better improvement in QoL parameters compared to their counterparts in the control groups(15).

The simulations for Holobalance intervention lay in the right lower quadrant of the cost-effectiveness graph which shows that this intervention is Dominant in all the simulations considered with a low cost and higher effectiveness. It is interesting to note that the ICER for all three countries is negative. However, in this case, it is irrelevant to consider the ICER (Incremental Cost-Effectiveness Ratio) for interpretation since the intervention (Holobalance technology) is dominant and there is no incremental cost incurred. Other studies have also noted that the use of virtual reality rehabilitation is cost-effective, as compared to standard fall prevention schemes of rehabilitation in the OTAGO system. (15).

For the different willingness to pay thresholds, Holobalance yields a lower loss in utility (40-50% lower) as a result of fall compared to Otago in the three countries. The Expected Incremental benefit (EIB) by implementing Holobalance in the three counties ranges from 225.5 Euro in Greece at a WTP value of 10000/QALY to 390.88 Euro in Germany at a WTP value of 30000/QALY. Generally, the EIB is higher in Germany compared to Italy and Greece and Greece has the lowest EIB among all.

Due to the fact that Holobalance is the dominant intervention in this analysis, the probability of cost-effectiveness i.e cost-effectiveness acceptability curve (CEAC) is 100% at all levels of WTP considered for all the countries. In a similar fashion, (16) the Expected value of perfect information (EVPI) is quite small and negligible in all the cases as well.

Considering all of these aspects, Holobalance holds the upper hand in achieving better and sustainable results. In this Bayesian Cost-Effectiveness Analysis, the Holobalnce technology is the dominant alternative with a lower cost and a higher level of effectiveness compared to the current standard therapy i.e Otago Exercise program. Moreover, Virtual reality (VR) based technologies have significant roles, particularly during COVID-19 because physical interaction is difficult (15). In this regard, Holograms for balance rehabilitation and fall prevention are crucial where exercise training and motivation can be performed from one's own home with remote monitoring at the same time solving the problem of staff shortage to implement personalized exercise programs with close monitoring. Thus, in an era of increased telemedicine use and personalized care, technologies such as Holobalance prove to be useful adjuncts to curb the growing threat of fall in the elderly population and the associated climbing costs.

The results obtained were confirmed by the quality responses received from three presentation HB in the workshops and focus group organized in Italy, Greece, and Germany with forty stakeholders of healthcare ecosystem, such as public healthcare managers, clinicians/technicians and private healthcare product and service companies. We have received positive feedback about the save cost of this new technology for fall prevention and the capacity to motivate the elderly to following the personalized exercises with HB platform.

Limitations

There was a limitation in data availability pertaining to the Holobalance technology considering its novelty and the small sample size of the data used in the analysis from the pilot study of the undergoing trial. The availability of country-specific figures and data to represent the relevant outcomes in the analysis was very challenging. Therefore, it was not possible to use specific values for the individual countries at the moment, but we'll develop the socio-economic and impact assessment when we'll have more pilot data and other sources available.

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