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Authors:

- **Manuela Deidda** Health Economics and Health Technology Assessment (HEHTA), Institute of Health and Wellbeing (IHW), University of Glasgow. Lilybank Gardens, G12 8RZ, Glasgow, UK. E-mail: Manuela.Deidda@glasgow.ac.uk telephone: 0141 330 5641 **(Corresponding author)**
- **Laura Coll-Planas** Fundació Salut i Envelliment – UAB. Universitat Autònoma de Barcelona. Institute of Biomedical Research (IIB Sant Pau), Barcelona, Spain.
- **Mark A. Tully** University of Ulster, Coleraine, Londonderry, UK.
- **Maria Giné-Garriga** Facultat de Psicologia, Ciències de l'Educació i de l'Esport Blanquerna Universitat Ramon Llull). C/ Císter 34, 08022 Barcelona, Spain.
- **Frank Kee** UKCRC Centre of Excellence for Public Health (NI), Centre for Public Health, School of Medicine, Dentistry and Biomedical Sciences, Queen's University Belfast, Belfast, UK.
- **Marta Roqué i Figuls** Fundació Salut i Envelliment - UAB. Universitat Autònoma de Barcelona. Institute of Biomedical Research (IIB Sant Pau), Barcelona, Spain.
- **Nicole E. Blackburn.** University of Ulster, Coleraine, Londonderry, UK.
- **Míriam Guerra-Balic** Facultat de Psicologia, Ciències de l'Educació i de l'Esport Blanquerna (Universitat Ramon Llull). C/ Císter 34, 08022 Barcelona, Spain.
- **Dietrich Rothenbacher** Institute of Epidemiology and Medical Biometry, Ulm University, 89081 Ulm, Germany.
- **Dhayana Dallmeier** Ulm University, Ulm, Baden-Württemberg, Germany; Agaplesion Bethesda Hospital, Geriatric Research Unit Ulm, Germany.
- **Paolo Caserotti** Syddansk Universitet, Campusvej 55 5230 Odense M, Denmark.
- **Mathias Skjødt** Syddansk Universitet Campusvej 55 5230 Odense M, Denmark.

- **Emma McIntosh.** Health Economics and Health Technology Assessment (HEHTA), Institute of Health and Wellbeing (IHW), University of Glasgow, UK.

On behalf of the SITLESS Consortium

Abstract

Background

This study details the within-trial economic evaluation and long term economic model of SITLESS, a multi-country, three-armed randomised controlled trial comparing a combined intervention of exercise referral schemes (ERS) enhanced by self-management strategies (SMS) against ERS alone and usual care (UC).

Methods

A cost-utility analysis, conducted from the base-case perspective of the National Health Service and personal and social services, estimated the incremental cost per incremental quality-adjusted life year (QALY) and years in full capability (YFC). A secondary analysis combined the costs with a broad set of outcomes within a cost-consequence framework, from a societal perspective. A Markov-type decision-analytic model was developed to project short-term changes in physical activity to long term outcomes and costs, over a 5 and 15 year time horizon.

Results

The results of the within-trial analysis show that SMS+ERS is highly likely to be cost effective compared to ERS alone (ICER €4270/QALY), but not compared to UC. Participants allocated to the SMS+ERS group also showed an improvement in YFC compared to ERS alone and UC. The long-term analysis revealed that SMS+ERS is likely to be a cost-effective option compared to ERS and UC over 5-year, but not with a 15 year horizon, being then dominated by ERS alone.

Conclusion

This research provides new evidence that SMS is a cost-effective add-on to ERS strategies. This economic evaluation informs the case for further, cost-effective, refinement of lifestyle change programmes targeted to older adults, with the aim of ultimately reducing the impact of non-communicable diseases in this population.

Keywords: cost effectiveness; healthy aging; exercise; public health; Europe

Introduction

Being insufficiently physically active is a known risk factor for major chronic diseases, disability and death, causing 9% of premature mortality worldwide[1]. In Europe, an inactive lifestyle resulted in a cost of 80.4 billion Euro in 2012[2]. In addition to low physical activity (PA), sedentary behaviour (SB), may also pose a significant health risk, independent of meeting the recommended levels of PA[3] . The cost impacts of prolonged SB to health services is also considerable, reaching £0.7 billion (approximately 0.8 billion Euro[4]).

Given the detrimental health and economic consequences of insufficient PA and high levels of SB, the evaluation and economic evaluation of interventions promoting active lifestyles is a key public policy research priority. This is increasingly relevant for the older population, who represent the fastest growing segment of the world population and account for almost 40% of the total healthcare expenditure across Europe[5].

An active lifestyle has been identified as a key modifiable factor to attenuate decline in physical and mental health in older adults [6] leading to healthy ageing trajectories[7] by increasing the odd of improving health and functioning. A recent systematic review[8] investigated the association between PA and healthy ageing, showing that adults engaged in high levels of PA have a 39% higher probability of living a healthy life than their inactive counterparts.

Indeed, increased PA and reduced SB in older adults prevent cognitive and functional decline, alleviate the symptoms of various chronic conditions associated to old age and might prevent or even reverse frailty[9]. This ultimately leads to improvements in the quality of life and wellbeing of older adults, and an 'active and healthy aging'[10].

In the last 20 years, exercise referral schemes (ERS) have become widely implemented in Europe as a public health programme to encourage an active lifestyle[11]. Within an ERS programme individuals assessed as insufficiently active are referred by primary care providers to PA programmes provided by a leisure facility or another third party service[12]. Although ERS have been demonstrated to be potentially effective and cost-effective in the older adult population over the short term[13-16], lack of commitment over the long term has been identified as a major barrier to the effectiveness and cost-effectiveness of ERS. In this regard, behavioural interventions in the form of self-management strategies (SMS) are aimed to increase motivation, thus promoting sustained behaviour change over time[17, 18]. SMS strategies have been found to be effective to reduce SB in adults [19] and in the older adults population[20]. However, evidence on the cost-effectiveness of SMS intervention in community-dwelling healthy older adults is scarce in the healthy ageing literature, since it focuses on the general adult population or those with chronic conditions[21, 22].

The SITLESS randomised controlled trial (RCT) aimed to determine whether and at what cost ERS can be enhanced by SMSs to reduce SB, increase PA, and improve markers of health, quality of life and function in community-dwelling older adults from four European countries, comparing a combined intervention of SMS+ERS against ERS alone and general recommendations about PA (usual care, UC). This paper reports the economic evaluation conducted alongside the SITLESS multinational RCT and includes a within-trial economic analysis, evaluating the cost-effectiveness of SMS+ERS vs. ERS and UC using an intention-to-treat (ITT) analysis and a long-term model extrapolating the cost-effectiveness results beyond the within trial component. A health economics protocol, describing the planned health economics analysis, has been published[23].

This appears to be one of the first economic evaluations assessing the value for money generated by a behavioural intervention targeting the older population in a multi-country European setting, thus generating increased understanding on the potential costs, cost savings and broader health and wellbeing outcomes generated by such intervention.

Methods

The SITLESS trial

SITLESS is a multi-country RCT with nested economic evaluation conducted in four centres located in four European countries: Belfast (UK), Barcelona (Spain), Ulm (Germany), Odense (Denmark). Community-dwelling adults aged 65+, insufficiently active and/or self-reporting spending more than six hours/day in SB, and without major physical limitations were randomised into three groups: SMS+ERS; ERS; UC.

The SMS+ERS participants received, concurrently to the 16-week PA programme offered to ERS participants, a 30 week SMS intervention encompassing a face to face visit, six group sessions and four telephone calls. Participants allocated to the UC control group were offered two health advice meetings with general recommendations on healthy lifestyle. Participants' assessments have been conducted at baseline, 4 months post intervention, month 16 (12 months post-intervention), and month 22 (18 months post-intervention). Full details of the RCT protocol are reported elsewhere[24].

Within-trial analysis

Economic evaluation frameworks

The main economic evaluation framework was a CUA, combining costs to the NHS and social care with Quality Adjusted Life Years (QALYs) and 'Years of full capability' (YFC)[25]. Results were reported in terms of the incremental cost per additional QALY/YFC generated by the intervention. A secondary analysis combined the costs and cost saving generated by the intervention with a broad set of effectiveness outcomes (health related, behavioural, functional) within a CCA framework[26, 27].

Using NICE guidance for the economic evaluation of public health interventions[27], the perspective of the National Health Service (NHS) and Personal Social Services (PSS) was used in the base case analysis, including costs related to usage of health care resources (GP, nurse, social worker, physiotherapist, occupational therapist, day hospital, psychiatrist, hospital outpatient clinic, A&E) and usage of social services (home care/home help, home meal delivery, day centre, meals provided at community centres, night care). A sensitivity analysis considering a broader societal perspective (i.e. accounting for care expenses sustained by individuals, besides those sustained by the NHS and social services[27]) was also conducted, adding the personal costs of attending exercise facilities, opportunity cost of exercise, additional costs associated with increasing PA/reducing SB and the cost of informal care.

Identifying, measuring and valuing costs and outcomes

Outcomes

The outcomes included in the CUA analysis were QALYs and YFC[28], calculated from EuroQol (EQ-5D-5L)[29] and the ICEpop CAPability measure for Older people (ICECAP-O)[28]. EQ-5D-5L and ICECAP-O scores were calculated at each time point and combined with time, using the area under the curve approach (AUC), to generate QALYs and YFC[25, 30]. Utility scores were calculated by mapping the 5L descriptive system data onto the 3L value set, using the country-specific 'crosswalk' value sets[31]. Given the multinational aspect of the analysis, in the base-case analysis, EQ-5D utility scores were derived using country-specific EQ-5D tariffs, which reflect country-specific differences in health perceptions and preferences. In the absence of country-specific utility weights to value ICECAP-O, UK value sets have been used for consistency across all 4 countries.

Costs

The cost of the SITLESS intervention and the comparators (ERS;UC) was collected using tailored cost logs, which captured the relevant centre-specific cost components, including actual costs (e.g. cost of the venue; number and type of staff involved in delivering the intervention; contact duration; travel costs sustained by participants and staff; average cost of the equipment used), as well as the opportunity costs (i.e. the foregone benefit of option not chosen), which was included in place of the actual cost in a deterministic sensitivity analysis. Specifically, the opportunity costs associated with the intervention costs (e.g. venue, travel time of staff) as well as the opportunity costs associated with the use of private resources (e.g. caregivers time; participants travel time) have been estimated. The opportunity cost of exercise reflects the value of time lost by participants participating in the SITLESS intervention, who could have used their time in a different way (working, doing other leisure time activities etc.). An average hourly wage rate was used to estimate this opportunity cost of time. The opportunity cost of the venue reflects the value of alternative usage of the venue (e.g. community activities, breastfeeding courses) to reflect the true cost of providing the SITLESS venue costs when rolled out.

Individual-level resource-use data were collected prospectively within trial at all relevant time points, using a data collection instrument tailored to capture country-specific differences (e.g. inclusion of country-specific examples of social-services) as well as usage of health and community services; use of exercise facilities; opportunity cost of exercise; additional costs sustained to increase PA/reduce SB. Following recommended practices to evaluate resources in multinational RCTs[32], a multi-country costing approach was adopted, using country-specific unit cost estimates to evaluate the resources used in the SITLESS countries.. All price weights were converted into a common currency (Euro) by use of Purchasing Power Parity (PPP)statistics reported by the OECD for a base year (2017). The OECD consumer price index for each country[33] was used to inflate unit costs estimates retrieved from previous studies.

Economic evaluation analysis methods

Incremental mean QALYs, YFC and costs between treatment groups were estimated on a multiple imputed dataset, adjusting for baseline utility and baseline covariates, using a multilevel GLM model (MGLM) to account for the complex hierarchical nature of the data as well as non-normality of outcomes.

A detailed description of statistical methods, including missing data imputation, has been included in supplementary appendix S1.

The incremental cost-effectiveness ratio (ICER), was calculated for the two comparison groups, providing an estimate of the additional cost per additional QALY (or YFC) generated by the SMS intervention. ICERs were plotted in the cost-effectiveness plane and compared with country-specific thresholds. Being an explicit Willingness to pay (WTP) threshold not available for all countries except UK, country-specific GDP/capita levels have been used[34], and cost-effectiveness is assessed by considering the highest and lowest thresholds. The cost/YFC ICER was compared against the £33,500-£36,150 threshold range estimated by Kinghorn and colleagues[35].

Long-term model

The long-term analysis explores the likely long-term cost-effectiveness of SMS+ERS beyond the 22 months' time horizon by extrapolating short-term changes in PA and SB into longer term outcomes (i.e. mortality, quality-adjusted life expectancy) and costs, considering a 5 and 15 years time horizon. A full description of the SITLESS Markov model has been included in Supplementary Appendix S2.

Sensitivity analysis

Probabilistic sensitivity analysis (PSA) was performed to quantify the joint effect of uncertainty around costs and QALYs [36]. Bootstrapping was used to generate 1000 cost-QALY pairs, which were then represented graphically in a cost-effectiveness plane and translated into cost-effectiveness acceptability curves (CEACs), indicating the probability that each intervention is cost-effective for a range of cost-effectiveness threshold values.

The deterministic sensitivity analysis explores several scenarios in, including: inclusion of a broader range of costs (societal perspective); inclusion of falls-related medical costs only; 20% variation around the cost of the SMS intervention; inclusion of the opportunity cost of the intervention (included as a 'proxy' cost, estimating the benefit foregone by using the resources to deliver the SITLESS intervention, as opposed to the actual cost); sensitivity of results to departures from the missing not at random hypothesis (MAR)

Results

Within trial

The average cost per person of the SMS and UC intervention is similar across countries, ranging from €121.9-141.3 (SMS) to €10.3-20 (UC). The ERS intervention shows a larger range (€112.3-239.4), with the lowest value seen in Spain (€112.3) mainly due to the absence of participants travel costs (all participants could walk to the sessions) and lower venue rental costs. The staff costs involved with delivering the intervention represents the main cost component, accounting for more than 50% of all country total costs. Tables 1, 2 and 3 in Supplementary Appendix S3 show a detailed breakdown of the cost of the SMS+ERS, ERS and UC intervention, respectively, for each country.

Cost Utility Analysis

Table 1 outlines the incremental costs and outcome (QALY and YFC) and the incremental cost-effectiveness ratio (ICER) for the comparisons SMS+ERS vs. UC and SMS+ERS vs. ERS.

As shown in Table 1, when controlling for baseline covariates, the participants randomised to SMS+ERS accrued greater incremental costs (€499) and also reported greater quality of life than participants randomised to UC. The probabilistic sensitivity analysis (Figure 1) reveals the majority of cost-effectiveness pairs lying in the north-east quadrant, showing little uncertainty regarding the improvement in quality of life associated with the SMS+ERS intervention. The ICER (€37,519/QALY)is above all the country-specific WTP threshold except the highest boundary. This is also reflected in the CEACs, where the probability of SMS+ERS being cost-effective compared to UC is below 42%.

The participants randomised to SMS+ERS accrued incremental costs of €114 and an incremental quality of life of 0.0267 compared to participants randomised to ERS. The cost-effectiveness plane reveals the majority of cost-effectiveness pairs lying in the north-east quadrant, showing little uncertainty regarding the improvement in quality of life associated with the SMS+ERS intervention combination. For the SMS+ERS vs. ERS comparison, the ICER (€4270/QALY), is below all the conventional cost-effectiveness thresholds. Considering the CEAC for this comparison (Fig. 1), SMS+ERS is the optimal intervention combination, with a likelihood of being cost effective above 85% for all the WTP threshold values. Table 1 also shows that participants in the SMS+ERS group reported a higher level of capability wellbeing (although not statistically significant) than participants randomised to ERS and UC. As shown in Supplementary Appendix S4, the cost-effectiveness results obtained in the base-case scenario are robust to several scenario analyses.

Considering the results for YFC, the estimated ICER for the SMS+ERS vs. UC comparison is €108478/QALY, which is above the YFC threshold range[35], whereas the ICER for the SMS + ERS vs. ERS comparison is €8571, which is below the YFC threshold range, making this option highly cost-effective. The likelihood of SMS+ERS being cost-effective ranges between 39% and 41% in the comparison with UC and between 91% and 92% in the comparison with ERS (Table 1).

[Table 1]

[Figure 1]

CCA

Table 2 shows the cost-consequence balance sheet, i.e. mean difference between arms at 22 months follow-up, in terms of costs and a broad set of efficacy outcomes

At 18 months post-intervention, participants allocated to the SMS+ERS arm showed on average lower, although not statistically significant, healthcare and societal costs than participants allocated to ERS and UC. Also, the SMS+ERS arm shows an improvement, albeit not statistically significant in most cases, in most of the outcomes, including an increase in the amount of time spent doing light, moderate and vigorous intensity PA; reduction of anxiety and depression; increase in independence; and improvement of social network. A reduction in SB is only observed when SB is objectively assessed with accelerometers). When self-reported SB is considered, a statistically significant reduction in the average number of hours spent doing sedentary activities is only observed in the comparison SMS+ERS vs. UC. A reduction in the fear of falling is also observed, but only in the comparison with UC arm.

[Table 2]

Long term model

Table 3 shows the long-term cost-effectiveness results for the base-case analyses. In the 5 year base-case scenario, total costs for the SMS+ERS group were €13,294 as compared to €13,326 in the ERS group and €13,347 in the UC group. SMS+ERS generates very small cost savings, compared to ERS (€32) and UC (€52). Total QALYs in the SMS+ERS group were 2.658, as compared to 2.6549 in the ERS group and 2.6526 in the UC group, resulting in a small gain of 0.0035 QALY per participant in the comparison SMS+ERS vs. ERS and 0.0058in the comparison SMS+ERS vs. UC. Being less costly and more effective, SMS+ERS dominates ERS and UC. In the 15 year base-case scenario, the total cost for the SMS+ERS group was €45,634 as compared to €45604(ERS) and €45628(UC). SMS+ERS has an incremental cost of €30 compared to ERS and €6 compared to UC. Total QALY in the SMS+ERS group were 6.957, as compared to 6.959 in the ERS group and 6.9538 in the UC group. This results in a small utility decrement of 0.002 in the comparison SMS+ERS vs. ERS and a utility gain of 0.0032 in the comparison SMS+ERS vs. UC. When considering a 15 year time horizon, SMS+ERS is dominated by ERS, being less effective and more costly. However, when comparing SMS+ERS with UC the ICER is €1960/QALY, which is below the conventional WTP thresholds, hence reflecting a cost-effective option. Compared to the 5 year scenario, SMS+ERS no longer dominates the comparators. This is due to the fact that the initial comparative advantage of SMS+ERS in terms of PA levels improvement, diminishes after the first year. , These results are robust to several scenario analyses (Supplementary Appendix S5).

[Table 3]

Discussion

The results of the short-term within-trial cost-effectiveness analysis reveal that adding the behavioural SMS component to the ERS intervention is cost-effective when compared to ERS alone. However, when comparing SMS+ERS vs. UC, SMS+ERS leads to small increases in quality of life and does not generate sufficient cost savings to be cost-effective. This result aligns with a previous trial[37] conducted in a younger population, that showed that advice and information on PA dominates exercise-referral programmes in terms of cost-effectiveness, while they were equal in terms of effectiveness on health outcomes. Also, the modest improvements in quality of life and cost savings generated by the intervention are in line with previous studies suggesting that the cost-effectiveness of such preventive interventions on a relatively healthy population is subject to considerable uncertainty, being strongly dependent on small changes in cost or outcome measures.

The descriptive evidence provided by the CCA suggest that in the 22 months follow up participants to the ERS+SMS intervention performed relatively better (albeit differences were not statistically significant) than those in the comparison groups across a preponderance of outcomes of interest including PA levels, SB, fear of falling, anxiety and depression, showing at the same time lower healthcare and social costs. Although in the absence of a formal rule to weight such 'consequences' the decision maker cannot formally appraise the results of the CCA (as for the CUA), the CCA provides complementary evidence on the broader benefits (beyond QALY and YFC) generated by SMS+ERS vs. comparisons.

The findings of the long-term cost-effectiveness analysis reveal that the SMS+ERS intervention combination is likely to be a cost-effective option compared to both ERS alone and UC in the medium term (5 years), but is dominated by ERS alone over a 15 years time horizon. Unlike other studies [38], the SITLESS model explicitly modelled decrease in the intervention effect over time, using transition rates across PA states calculated within-trial. This is a strength of our analyses, which has benefitted from a follow-up period greater than one year to model the decay of the intervention. Also, when comparing SMS+ERS to UC, SMS+ERS generates improvements in QALY and cost savings, but there is considerable uncertainty, reflected in a relatively low probability of cost-effectiveness, which prevent us to conclude that the intervention is cost-effective. Amongst the limitations of the long-term model cost-effectiveness analysis, the assumptions made in relation to the decay of the intervention effect over time have a strong impact on the cost-effectiveness results. Also, while base-case results seem to suggest evidence of cost-effectiveness of SMS+ERS vs. both comparators, the QALY improvements and costs savings are modest. Therefore, even in the most favourable scenario, such small changes in costs and QALY might not justify implementing a resource-intense intervention as the SMS+ERS intervention.

Borrowing insights from social cognitive theory, the SITLESS trial added a behavioural component, in the form of SMS, to the already existing ERS schemes, but heterogeneously implemented across European countries.

The economic evaluation alongside SITLESS is the first economic evaluation to assess the value added by a behavioural intervention to ERS, in a population of a community-dwelling older adults, as compared to ERS alone and UC, adopting a methodology suited to the economic evaluation of a complex public health intervention[39] This is the first multi-country study of its type, exploring a heterogeneous setting in terms of cultural values, attitudes towards physical exercise, healthcare and social settings and generating potentially generalisable results. We

Overall, this research provides new evidence that SMS+ERS, compared to ERS alone, is likely to generate value for money in the short term, in terms of improvements in quality of life, wellbeing and capability. Also, SMS+ERS has the potential to be cost-effective compared to ERS alone and UC (which is a dominated intervention) in a medium-term time horizon (5 years), generating modest increases in QALY and cost savings, although

benefits and cost savings are not likely to be sustained in the longer term, due to an expected reduction over time in the rate of participants moving to a higher PA level in the SMS+ERS group compared to ERS and UC.

It's worth noting that the cost-effectiveness results are based on commonly accepted NICE thresholds (£20,000-£30,000). Using a 'supply-based' threshold of £12,000[40] the SITLESS intervention is less likely to be cost-effective.

Considering this, European decision-makers may consider the incremental cost per QALY worth the investment, supporting the enhancement of ERS interventions - often implemented as part of public health programmes - with a SMS behavioural component as a likely highly cost-effective strategy within a community-dwelling 65+ European population.

The evidence generated from the SITLESS trial provides new economic evidence for investing in interventions to increase PA and reduce SB thereby reducing the impact of non-communicable diseases in this population. This will allow the further refinement of lifestyle change programmes targeted to older adults, grounded on the behavioural theory.

Conflict of interest

None declared.

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Key points

- First multi-country economic evaluation of a complex, public health intervention to assess the value added by a behavioural intervention to ERS in a population of a community-dwelling older adults.
- SMS + ERS is not a cost-effective intervention compared with UC but is a cost-effective add on when compared with ERS alone.
- SMS+ERS has the potential to be cost-effective compared to ERS alone and UC in a medium-term time horizon (5 years), generating modest increases in QALY and cost savings, but not in the long term (15 years), due to a decadence of the intervention effect.
- European health care decision-makers now have strong evidence to support the enhancement of existing ERS public health programmes with an SMS behavioural component as a likely highly cost-effective strategy within a community-dwelling 65+ European population
- Further strategies should be added and tested to maintain improvements in SB and PA levels over longer periods of time.

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Table 1 Incremental cost and outcome (QALY, YFC) summary, SMS+ ERS vs. UC; SMS+ ERS vs. ERS

Within trial cost, QALY, YFC and ICER (SMS+ERS vs. UC)										
COST/QALY										
	Arm						**Probability SMS+ERS cost effective**			
	ERS+SMS	**UC**	**Difference**	**95% bootstrapped CI**		**ICER**	**WTP € 20,433**	**WTP € 30,650**	**WTP € 27,300**	**WTP € 37,700**
Cost (€)	3171	2672	**499**	*-56*	*1143*	**37519**	**22%**	**35%**	**31%**	**42%**
QALY	1.449	1.4357	**0.0133**	*-0.015*	*0.036*					
COST/YFC										
	ERS+SMS	**UC**	**Difference**	**95% bootstrapped CI**		**ICER**	**Probability SMS+ERS cost effective**			
							WTP £34,255		**WTP £36,932**	
Cost (€)	3171	2672	**499**	*-56*	*1143*	**108478**	**39%**		**41%**	
YFC	1.4957	1.4911	**0.0046**	*-0.013*						
Within trial cost, QALY, YFC and ICER (SMS+ERS vs. ERS)										
COST/QALY										
	Arm						**Probability SMS+ERS cost effective**			
	ERS+SMS	**ERS**	**Difference**	**95% bootstrapped CI**		**ICER**	**WTP € 20,433**	**WTP € 30,650**	**WTP € 27,300**	**WTP € 37,700**
Cost (€)	3171	3057	**114**	*-424*	*626*	**4270**	**86%**	**91%**	**89%**	**92%**
QALY	1.449	1.4223	**0.0267**	*-0.001*	*0.055*					
COST/YFC										
	ERS+SMS	**ERS**	**Difference**	**95% bootstrapped CI**		**ICER**	**Probability SMS+ERS cost effective**			
							WTP £34,255		**WTP £36,932**	
Cost (€)	3171	3057	**114**	*-424*	*626*	**8571**	**91%**		**92%**	
YFC	1.4957	1.4824	**0.0133**	*-0.004*	*0.036*					

Table 2 Cost-consequence balance sheet, 18 months follow-up

	SMS+ERS vs. ERS	*Improvement*	SMS+ERS vs. UC	Improvement
Incremental Costs				
Healthcare perspective	**€- 97.4 (378.9)**	***Yes***	**€ - 90.1 (372.02)**	***Yes***
Societal Perspective	**€ - 526 (864.9)**	***Yes***	**€ - 609.5 (729.9)**	***Yes***
Intervention cost	**€100.16 (3.09)**	***No***	**€ 296.4 (1.98)**	***No***
Incremental Consequences				
% Sedentary time	**-0.457 (0.739)**	***Yes***	**-0.817 (0.761)**	***Yes***
% Moderate-Vigorous Activity	**0.109 (0.262)**	***Yes***	**0.177 (0.242)**	***Yes***
% Light Activity	**0.349 (0.588)**	***Yes***	**0.642 (0.635)**	***Yes***
Time sedentary (Hours/week, self-reported)	**0.142 (0.231)**	***No***	**-0.328* (0.253)**	***Yes***
Anxiety score (HADS)	**-0.235 (0.374)**	***Yes***	**-0.172 (0.398)**	***Yes***
Depression score (HADS)	**-0.019 (0.335)**	***Yes***	**-0.255 (0.359)**	***Yes***
Activities of daily living (ADL) score	**-0.304 (0.369)**	***Yes***	**0.161 (0.324)**	***No***
Falls efficacy scale (FESI) score	**0.013 (0.381)**	***No***	**-0.066 (0.385)**	***Yes***
Social network score (Lubben)	**0.515 (0.642)**	***Yes***	**0.317 (0.778)**	***Yes***

Notes: *SBQ: sedentary behaviour questionnaire, self-reported hours/day of SB; scale 0-24.*
HADS: anxiety and depression score; scale: 0 (no anxiety)-21.
FESI: short falls efficacy; scale: 7 (no fear of falling)- 28.
ADL: activities of daily living; scale 0 (independence)- 24.
Lubben social network scale: measures social isolation; scale: 0 (greater social isolation)- 30.
Standard errors reported in parentheses.
**Significance at 10% level.*

Table 3 Incremental costs, incremental QALY and ICER for the base-case scenario

	Arm	Total Cost (€)	Total QALY	Comparison	Incremental Cost (CI)	Incremental QALY (CI)	ICER
5 YEARS Time horizon **Base-case analysis**	**SMS+ERS**	13,294	2.6584				
	ERS	13,326	2.6549	SMS+ERS vs ERS	-32 (-61:140)	0.0035 (-0.0071; 0.0150)	***SMS+ERS dominates***
	UC	13,347	2.6526	SMS+ERS vs. UC	-52 (-179;50)	0.0058 (-0.0045; 0.0189)	***SMS+ERS dominates***
15 YEARS Time horizon **Base-case analysis**	**SMS+ERS**	45,634	6.9570				
	ERS	45,604	6.9590	SMS+ERS vs. ERS	30 (-186; 249)	-0.0020 (-0.0355; 0.0330)	***SMS+ERS is dominated***
	UC	45,628	6.9538	SMS+ERS vs. UC	6 (-236; 255)	0.0032 (-0.0336; 0.0405)	***1960***

Notes: credibility interval in parenthesis

Supplementary Material

Supplementary Appendix S1: within-trial analysis: statistical and econometric methods

Economic evaluation analysis methods

Outcomes and costs were analysed using multivariate, multilevel mixed-effects generalized linear model (MGLMs), adjusting for baseline characteristics. MGLMs allow the inclusion of both fixed effects and random effects, accounting at the same time for non-normality of costs and outcomes.

The choice of the statistical model to analyse cost and outcome data in SITLESS was driven by the existence of two levels of clustering. First, cluster at couple level: cohabiting individuals have been randomised together, implying a substantial correlation between subjects that needs to be considered. In addition, clustering at country level: the multicountry nature of the SITLESS intervention does require the between vs. within country correlation to be explicitly tackled. Cost and outcome data thus fall naturally in a complex hierarchical structure with three levels of nesting: individuals are nested within couples and couples are nested within countries. Using a multilevel model allows the correlation structure between participants and higher level units (couples and countries) to be explicitly modelled[1], tackling explicitly the lack of independence of errors between the observations. Specifically, the outcomes and cost equation in the SITLESS analysis were analysed modelling countries as fixed effects and couples as random effects. A robustness analysis was performed including both couples and country as random effect, and including only country random effects, showing no significant differences in results. Also, the intra-class correlation between costs and outcomes in the same centre was very low, indicating that between-countries variation is not an important component of the total variation, i.e. countries do not differ substantially in measured outcomes and costs. The likelihood ratio test (which tests the null hypothesis of random effects being zero) reject the null hypothesis, thus providing evidence against the inclusion of random effects at country level. Following Briggs, Glick [2], a joint tests of significance for treatment-by-country interactions in the outcome and cost model was performed, to look for evidence of heterogeneity across countries for treatment effects in QALY or total costs, showing no significance, overall, of the treatment-centre interaction. This is in line with Drummond, Barbieri [3], who state that MLM may not be required when the number of countries in the trial is less than five. In this case, the level of within-country variability will be low relative to the between-country variability, providing evidence of low between-country heterogeneity. In this case, it's likely that the pooled estimation would adequately represent the intervention effect across countries. Also, it is likely that the within-couples clustering effect plays a more important role in relation to costs, QALY and YFC than within-country heterogeneity.

The modified Park test was conducted to choose the best family, while a battery of test (Pearson correlation tests, Pregibon Link test and Modified Hosmer and Lemeshow test) were used to guide the choice of the best family. The Gamma family with log link was chosen for total costs and total YFC, while Poisson with log link was found to be the best fit for Total QALY, as these were the best fit according to the tests. Baseline costs, baseline EQ5D and ICECAP-O scores were included as covariate in the total cost, total QALY and total YFC regressions respectively, to account for potential imbalance in baseline utility, capability or resource use level [4]. All regressions were adjusted for baseline characteristics, including age, gender, marital status, education, a dummy indicating whether the individual lives alone and number of comorbidities.

All within-trial analyses were performed using Stata version 16.

Missing data

Following best practice [5] a thorough analysis has been performed in order to assess the extent of missingness, as well as the missing data mechanism. Total costs and total QALYs are cumulative quantities hence any missing data at any of the follow-up points results in those patient's data being removed from the complete-case analysis. Further, since total QALY/YFC and total costs have been adjusted for baseline characteristics, those patients with missing values in any of the covariates which have been used in the regression have been dropped as well. Complete-case analysis consisted of the patients with completed data on baseline characteristics, who completed all EQ-5D and ICECAP-O profiles and have completed resource use data at each time point. Overall, there were 620 participants in the complete-case analysis (185 randomised to UC, 213 to ERS and 222 to SMS+ERS).

Table 1 below shows the percentage of missing data, by intervention arm, for baseline characteristics and total cost and outcomes (EQ5D and ICECAP-O scores), at each time point. The number of questionnaires returned at each follow-up point decreased with time: the percentage of missingness goes from less than 5% at baseline to almost 48% in the last follow-up. The table shows a consistent pattern across costs and outcomes, with a higher percentage of missing value in the UC arm. A proportion of missing data which differs by treatment allocation and across timepoints suggests that data are unlikely to be MCAR, making complete-case analysis biased. We further investigate the mechanism of missingness by assessing whether a significant association exist between: a) probability that total costs and outcomes are missing and baseline covariates; b) probability to observe missing observed outcomes and costs and previously observed outcomes and costs, finding that the probability of observing missing costs and outcomes is significantly associated with both baseline characteristics and, in most cases, with previously observed values of costs and outcomes, thus ruling out the possibility that data are MCAR and CD-MAR. The reasons discussed above, and, the large proportion of data lost for the complete-case analysis strengthen the rationale for using the multiple imputation data sets in the base case. While the analysis on the imputed dataset was performed as a base-case analysis, a sensitivity analysis considering a complete-case analysis was also performed.

Deterministic mean imputation was used to predict missing data at baseline[6]. Multiple imputation procedures using chained equations were used to impute follow-up missing data separately for each arm of the trial, creating 60 imputed datasets. Compared to other methods (e.g. mean imputation; last value carried forward), multiple imputation incorporates uncertainty associated with missing data, thus providing unbiased results[7]. Predictive mean matching has been used in order to deal with non-normality of cost and outcome data[5]. Schomaker and Heumann [8] approach (MI boot) procedure was used to calculate bootstrapped confidence intervals. This approach has been proved to yield valid inference when dealing with multiple imputed data.

Cost-effectiveness results obtained with the multiple imputation procedure strongly rely on the validity of the MAR assumption[5]: individuals who completed and returned all questionnaires are similar to the individuals who did not, conditional on their observed characteristics. However, this may not be the case: patients with missing quality of life, capability or cost data might be those with lower (or higher) quality of life or capability and accrued higher (or lower) healthcare and social costs. Sensitivity analysis on the multiple imputation model has been thus performed to test how sensitive the cost-effectiveness results are to the MAR assumption, exploring sensitivity of results to departures from MAR [9]. Multiple imputation was performed in STATA 16, using the programme 'mi impute chained'.

Table 1: Missing data, by arm.

Percentage of missing data, by arm			
	UC	**ERS**	**ERS+SMS**
Outcomes			
EQ5D score -baseline	5.46	3.58	4.18
EQ5D score -post intervention	34.06	20.13	23.08
EQ5D score -12m	49.13	37.36	37.58
EQ5D score -18m	47.82	39.82	39.12
ICECAP-O score - baseline	6.99	4.7	5.05
ICECAP-O score - post intervention	34.93	20.13	23.3
ICECAP-O score -12m	49.34	37.81	37.58
ICECAP-O score - 18m	47.82	40.04	39.56
Costs			
total cost1-baseline	1.31	0.67	0.44

total cost1-post intervention	31.44	17.9	21.32
total cost1-12m	47.16	34	34.51
total cost1-18m	46.07	38.03	37.36
total cost2-baseline	1.31	0.67	0.44
total cost2 -post intervention	31.44	17.9	21.32
total cost2-12m	47.16	34	34.51
total cost2 -18m	46.07	38.03	37.36
total cost3-baseline	1.31	0.89	0.44
total cost3-post intervention	30.79	17.9	21.54
total cost3-12m	47.16	34	34.51
total cost3-18m	46.07	38.03	37.36
Baseline covariates			
age	0.22	0	0
male	0	0	0
marital	5.68	2.46	3.3
education	2.18	2.01	1.32
Living alone	5.68	2.68	3.08
comorbidity	5.46	1.57	3.96

Supplementary Appendix S2: The SITLESS long-term model

(1) Model structure

The SITLESS model is a Markov-type model projecting short-term changes in PA into longer terms outcomes (i.e. mortality, quality-adjusted life expectancy) and costs. The model simulated a cohort of community-dwelling adults aged 65+ years and includes eight mutually exclusive states (two physical activity states and six disease states) and death (an absorbing state).

The SITLESS long-term model has been adapted from existing models [10, 11] to account for the specificities of the SITLESS target population, including ageing-specific health outcomes and transition probabilities, informed by an 'ad hoc' systematic review.

Figure 1 shows the structure of the Markov model and Table 1 below shows the key assumptions underlying the model. The model has been developed using Microsoft Excel. We tested internal and face validity of the model

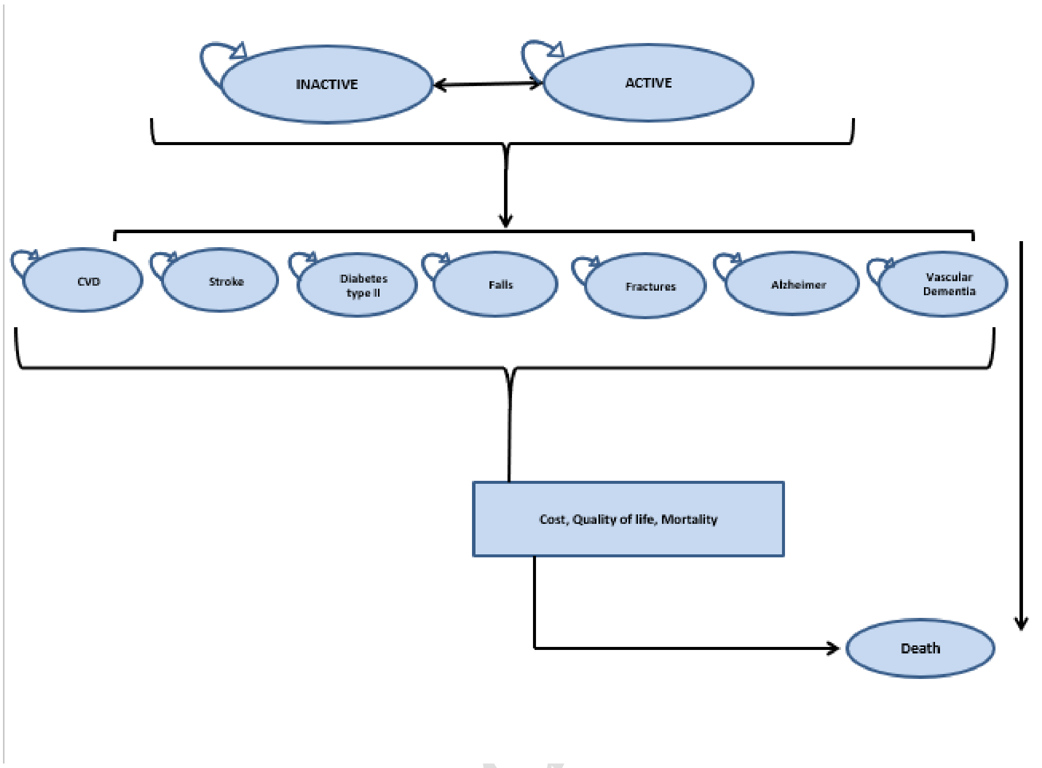
Table 3: Model assumptions

Physical activity states	Physical activity has been classified into two health states using the metabolic equivalent (MET) as a unit of measurement that expresses the energy cost of physical activity. In consideration of the physical activity recommendations for elderly adults [12], two physical activity states were included in the model: 'active' (>7.5 MET/hours/week, corresponding to 150 minutes of moderate intensity aerobic activity or 75 minutes of vigorous activity) and 'inactive' (<7.5 MET/hours/week).
Health states	The health states represent seven health conditions associated with a lack of physical activity in the older population: coronary heart diseases, stroke, type 2 diabetes, vascular dementia, Alzheimer`s disease, falls and fractures. The diseases to be included in the model were chosen – among the list of high-incidence diseases amongst the 65+ population - considering those for which an inactive lifestyle represented a key risk factor. Only final diseases and conditions (e.g. fractures, stroke), rather than intermediate states (e.g. osteoporosis, high blood pressure), were considered. The final set of diseases included in the model was co-created and validated by the SITLESS collaborators.
Transition between model states	At the beginning of the model, all members of the cohort were well and did not suffer from any of the diseases included in the model. Individuals start in a physical activity state, and at the end of the first cycle, participants can either stay in the same physical activity state, move to a different physical activity state, to a disease state or death. Once in a disease state, participants can either stay in the same disease state or move to the death state. While this assumption rules out the possibility that participant have more than one disease, comorbidities – which are common among the older adult population- have been taken into account in a sensitivity analysis, applying a utility decrement [80].
Transitions between PA states	Calculated using the SITLESS RCT data; • First year: probability of moving to a different PA state or staying in the same state considering the transitions between baseline and 4 months (post-intervention). • After the second year, as it is plausible to assume a decline in PA over time, we used the transitions between 4 months and 18 months follow-up to calculate transition probabilities.
Time horizon	a) 5 years; b) 15 years.
Cycle length	1 year

Time and cross-country adjustment	All costs included in the model are reported in Euros and adjusted using purchasing power parity (PPP) for a base year (2017). Costs and benefits are discounted at 1.5% per year [13].

Notes: One MET is defined as the 'resting metabolic rate' and is equivalent to consuming 3.5 mm of oxygen per kilogram of body weight.

Figure 1 Markov model



(2) Model parameters

The parameters to populate the model have been retrieved from several sources, including the SITLESS RCT and 'ad hoc' systematic and scoping reviews.

Specifically:

- **Disease risk**

A systematic literature review was conducted to obtain an estimate of the risk of developing each of the chronic diseases identified as being relevant for the SITLESS 65+ target population by PA level.

A preliminary scoping review identified a set of chronic diseases associated with lack of physical exercise in older adults. The results of the review were validated through an expert opinion, in collaboration with the SITLESS team. The final set of diseases includes:

- Stroke
- Cardiovascular disease
- Alzheimer disease
- Vascular dementia
- Falls
- Fracture

– Diabetes type II

The search has been performed in 5 databases: Medline, Embase, Cochrane, Web of Science, Psychinfo and Sportdiscus. The search retrieved 23730 papers; after deleting 3790 duplicates, we end up with 19940 records.

The search was conducted in three phases:

1. Title screening: after excluding clearly irrelevant titles, 3052 abstracts were selected for abstract screening;

2. Abstract screening: we selected prospective studies discussing the impact of physical activity and sedentary behavior upon the risk of developing the previously identified diseases; 418 papers were selected for full text screening.

3. Full text screening:

a. we included only those studies not fulfilling the inclusion criteria. Specifically, we excluded papers: where the age at baseline was lower than 65, papers considering occupational activity only or where the impact of occupational activity could not be separated from leisure time activity; abstracts-only, conference proceedings or posters; cross-sectional studies.

b. We further excluded: papers where the risk of incident case of the disease was not specified; studies where physical activity was not assessed in METs (Metabolic equivalents), or in Kcal, times or intensity of physical exercise, which could be converted in MET; studies where the thresholds to identify physical activity levels were not stated (e.g. physical activity was classified as 'high' and 'low', without a quantification of PA states in terms of METs, duration or Kcal).

We finally included 12 papers discussing the differential risk of developing a disease based on physical activity levels including: 3 papers on CVD; 4 papers on Alzheimer; 3 papers on vascular dementia; 1 paper on falls; 1 paper on fracture.

No studies on diabetes and stroke fulfilled the inclusion criteria. Two studies considering a lower age threshold (60) have been thus retrieved from the literature search results. Among the included studies, only one study considered the impact of SB upon the risk of developing a disease [14].

Following the physical activity recommendations for older adults, two physical activities states were identified in the model: active, corresponding to at least 7.5 MET/hours/week, and inactive. The physical activity levels and corresponding incident cases reported in the studies have thus been aligned with the chosen 'active' and 'inactive' states. Specifically, for each category of PA reported in the study, a midpoint was calculated; incident cases were aggregated when necessary and allocated into the 'active' and 'inactive' group.

Physical activity levels were expressed in METs/hour/week using consistent conversions across all the studies. When physical activity levels were reported in terms of duration, frequency and intensity, these have been converted into METs using 6 METs as the score for vigorous or strenuous intensity activity and 3 METs for moderate intensity activity[15]. When physical activity was reported in terms of type of activity (e.g. walking, sport activity), these were mapped into MET level using standard classification codes[15]. In few instances[16, 17] physical activity was reported in terms of distance or time spent walking; in absence of information on intensity, a MET equal to 1.8 was used. When physical activity levels were reported in terms of Kcal, the UK national average of body weight was used for the conversion into METs.

A meta-analysis with random effect was carried out separately for each disease (CVD, Alzheimer, vascular dementia).

While the original scope of the review was to identify the joint effect of PA and SB (rather than their independent contribution) on the risk of developing chronic diseases, the evidence available for the 65+ population subgroup was limited: most of the retrieved papers estimated the disease risk given PA levels; only a few of them considered the impact of SB, whereas none of them considered their joint impact. In consideration of the limited evidence available for the older segment of the population, after applying the exclusion criteria, we included only papers considering PA. The complementary effect of SB has been taken into account in a scenario analysis, by applying a mortality correction [18].

- **Transitions between physical activity states**

Transitions between PA states, as well as the proportion of participants starting in the 'Active' and 'Inactive' states were calculated from the SITLESS RCT data. Although in the SITLESS trial, PA and SB have been assessed objectively (using Actigraph) and subjectively, the model employed the subjective measures of PA and SB for two main reasons: 1) hours of moderate and vigorous PA recorded by the accelerometer need to be adjusted by the wearing time, thus making it difficult comparisons across arms and time; 2) much of the evidence linking PA to disease risk uses self-reported measures, rather than objectively measured PA/SB [19].

- **Quality of life**

Utility values for the inactive and active states were calculated from the EQ-5D utility scores reported in the SITLESS RCT data.

To obtain the utility values associated with the chronic conditions considered in the model a scoping literature review was conducted. Amongst the studies identified by the review, systematic reviews were used in the first instance, if available (e.g. [20]); otherwise, parameters were retrieved from studies where the target population was close to the age of the SITLESS participants. Only when utility values for the 65+ population were not available, general adult population parameters were used.

- **Costs**

The costs associated with health states included in the model were retrieved from the literature, considering cost estimates including both direct medical costs and broader societal costs.

- Mortality

Mortality risk was estimated as an adjusted risk based on all-cause mortality combined with the age structure for the population[21], whereas cause-specific mortality risk was based on literature estimates (Table 2)

Table 2 summarises the parameters which have been used in the Markov model.

Table 2 Markov model input parameters

Model Parameters	Value	Distribution	95% CI		SD	Source
			Lower	Upper		
Transition probabilities (First year)						
Physical activity states						
SMS+ERS						
Inactive to inactive						
Inactive to recommended activity	**0.54**	Lognormal	0.44	0.64		SITLESS RCT
Recommended activity to inactive	**0.25**	Lognormal	0.18	0.32		SITLESS RCT [22]
ERS						
Inactive to recommended activity	**0.48**	Lognormal	0.38	0.57		SITLESS RCT [22]
Recommended activity to inactive	**0.35**	Lognormal	0.27	0.44		SITLESS RCT [22]
UC						
Inactive to recommended activity	**0.41**	Lognormal	0.27	0.56		SITLESS RCT [22]
Recommended activity to inactive	**0.40**	Lognormal	0.29	0.50		SITLESS RCT [22]
Transition probabilities (Year 2 and following)						
Physical activity states						
SMS+ERS						
Inactive to recommended activity	**0.29**	Lognormal	0.22	0.37		SITLESS RCT [22]
Recommended activity to inactive	**0.16**	Lognormal	0.12	0.21		SITLESS RCT [22]
ERS						
Inactive to recommended activity	**0.40**	Lognormal	0.32	0.48		SITLESS RCT [22]
Recommended activity to inactive	**0.18**	Lognormal	0.13	0.23		SITLESS RCT [22]
UC						
Inactive to recommended activity	**0.30**	Lognormal	0.23	0.38		SITLESS RCT [22]
Recommended activity to inactive	**0.14**	Lognormal	0.10	0.20		SITLESS RCT [22]
Transition probabilities						
Health States						
Inactive to CVD	**0.0410**	Lognormal	0.0279	0.0564		meta-analysis[14, 23, 24]
Recommended activity to CVD	**0.0255**	Lognormal	0.0172	0.0353		
Inactive to Alzheimer	**0.0110**	Lognormal	0.0088	0.0135		meta-analysis[16, 25, 26]
Recommended activity to Alzheimer	**0.0084**	Lognormal	0.0059	0.0111		
Inactive to Dementia	**0.0057**	Lognormal	0.0013	0.0129		meta-analysis[16, 25, 27]
Recommended activity to Dementia	**0.0041**	Lognormal	0.0004	0.0114		
Inactive to Falls	**0.1085**	Lognormal	0.1039	0.1131		Buchner, Rillamas-Sun [28]
Recommended activity to Falls	**0.0776**	Lognormal	0.0753	0.0799		
Inactive to Fractures	**0.0019**	Lognormal	0.0012	0.0026		Buchner, Rillamas-Sun [28]
Recommended activity to Fractures	**0.0017**	Lognormal	0.0013	0.0021		
Inactive to Stroke	**0.0069**	Lognormal	0.0056	0.0083		Jefferis, Whincup [29]

Recommended activity to Stroke	**0.0066**	Lognormal	0.0052	0.0080		
Recommended activity to Diabetes	**0.0049**	Lognormal	0.0047	0.0050		InterAct Consortium [30]
Inactive to Diabetes	**0.0034**	Lognormal	0.0033	0.0034		
Costs (Annual cost, 2017, €)						
Cost associated with diseases (Societal perspective)						
CVD	**4,746**	fixed				Liu, Maniadakis [31]
Alzheimer	**29,158**	fixed				Wimo, Reed [32]
Dementia	**23,190**	fixed				Sicras, Rejas [33]
Falls	**4,444**	fixed				Hartholt, van Beeck [34]
Fractures	**13,078**	fixed				Hartholt, van Beeck [34]
Stroke	**43,938**	fixed				Patel, Berdunov [24]
Stroke (after 1st year)	**29,203**	fixed				Patel, Berdunov [24]
Diabetes	**7,409**	fixed				Hex, Bartlett [35]
Cost of the SITLESS intervention and control (cost/person)						
SMS+ERS	**286**	fixed				SITLESS RCT[22]
ERS	**186**	fixed				SITLESS RCT [22]
UC	**18**	fixed				SITLESS RCT [22]
Utility values						
Disease			**r(α)**	β		
Alzheimer`s disease	**0.60**	Gamma	100.000	0.006	0.06	Vandepitte, Putman [36]
Dementia	**0.75**	Gamma	9.000	0.083	0.25	Orgeta, Edwards [37]
Falls	**0.62**	Gamma	7.267	0.085	0.23	Bjerk, Brovold [38]
Fractures (disutility)	**0.14**					Karnon, Afzali [39]
Stroke	**0.62**	Gamma	3.33	0.19	0.34	Pickard, Johnson [40]
CVD	**0.72**	Gamma	8.73	0.08	0.243	Lacey and Walters [41]
Diabetes	**0.77**	Gamma	8.133	0.095	0.27	Clarke, Gray [42]
Physical activity states						
Inactive	**0.760**		0.736	0.784	0.012	SITLESS RCT [22]
Recommended activity	**0.797**		0.776	0.817	0.010	SITLESS RCT [22]

Mortality						
Inactive to death	0.0150	Fixed				Ekelund, Tarp [18]
Recommended activity to death	0.0050	Fixed				Ekelund, Tarp [18]
Background mortality	***Age-specific, Life Tables***					ONS [21]
Alzheimer to death	0.074	Fixed				Garcia-Ptacek, Farahmand [43]
Dementia to death	0.160	Fixed				Garcia-Ptacek, Farahmand [43]
Falls to death	0.010	Fixed				Dunn, Rudberg [44]
Fractures to death	0.235	Fixed				Dunn, Rudberg [44]
Stroke to death	0.4	Fixed				Brønnum-Hansen, Davidsen [45]
CVD to death	0.002	Fixed				Wilmot, O'Flaherty [46]
Diabetes to death	0.015	Fixed				Hendriks, van Hateren [47]

Supplementary Appendix S3. The cost of the SITLESS intervention

Tables 1, 2 and 3 show the breakdown of the SMS, ERS and UC costs, as well as the mean total cost and cost/participant of the SMS, ERS and UC intervention, respectively, for each country. The total cost and cost/participant calculated considering the opportunity cost (i.e. benefit foregone) in terms of venue, participants and staff travel cost is also shown. All costs have been reported in Euros, and adjusted using PPP for a base year.

Table 1 Cost of the SMS intervention, by centre

SMS INTERVENTION	**TOTAL COST (PPP adjustment for values in £) Values in € 2017**			
COST CATEGORY	**ODENSE**	**BARCELONA**	**BELFAST**	**ULM**
N	113	118	108	116
Venue				
Opportunity cost	3481.1	3726.1	2623.5	2437.7
Rent cost	0.0	0.0	0.0	180.0
Staff Cost				
Individual session	3382.2	3154.7	3135.0	2455.0
Group sessions	2668.4	3317.6	1952.0	2153.9
Telephone calls	3828.3	3445.6	2508.0	4110.4
Travel costs				
Travel cost (staff)	58.1	213.3	244.1	48.4
Travel cost staff opportunity cost	5237.2	1391.3	207.5	72.6
Travel cost (participants)	1877.3	0.0	6142.0	3980.0
Travel cost (participants opportunity cost)	2006.9	1544.6	580.9	368.3
Equipment				
Equipment	2048.0	4249.8	1278.0	1656.5
Other costs	0.0	0.0	0.0	0.0
Total cost (I)	**13862.3**	**14381.0**	**15259.0**	**14584.2**
Cost/participant (I)	**122.7**	**121.9**	**141.3**	**125.7**
Total cost (II) (including travel and venue opportunity cost)	**22652.0**	**20829.7**	**12284.8**	**13254.3**
Cost/participant (II)	**200.5**	**176.5**	**113.7**	**114.3**

Table 2 Cost of the ERS intervention, by centre

ERS INTERVENTION	**TOTAL COST (PPP adjustment for values in £) Values in € 2017**			
COST CATEGORY	**ODENSE**	**BARCELONA**	**BELFAST**	**ULM**
N	112	118	104	113
Venue				
Opportunity cost	8320.0	6800.0	7192.6	5866.7
Rent cost	2164.5	0.0	0.0	1760.0
Staff Cost				

Group sessions	14450.7	11810.6	12227.5	10189.6
Telephone calls	972.6	205.0	43.4	359.0
Travel costs				
Travel cost (staff)	1664.0	850.0	1764.9	352.0
Travel cost staff opportunity cost	597.3	1574.8	2678.9	4075.8
Travel cost (participants)	7168.0	0.0	9251.2	7232.0
Travel cost (participants opportunity cost)	10035.2	7723.9	969.0	10570.8
Equipment				
Equipment	188.8	199.0	175.3	190.5
Other costs				
Other costs	208.4	191.1		17.4
Total cost (I)	**26817.1**	**13255.6**	**23462.4**	**20100.4**
Cost/participant (I)	**239.4**	**112.3**	**225.6**	**177.9**
Total cost (II) (including travel and venue opportunity cost)	**34773.1**	**28504.3**	**23286.9**	**31269.7**
Cost/participant (II)	**310.5**	**241.6**	**223.9**	**276.7**

Notes: travel cost of participants in Barcelona are zero since all participants walked to the exercise facility (the primary health care centre located in their neighbourhood). The category 'other cost' includes the preparation time for trainers.

Table 3 Cost of the UC intervention, by centre

UC INTERVENTION	**TOTAL COST (PPP adjustment for values in £) Values in € 2017**			
COST CATEGORY	**ODENSE**	**BARCELONA**	**BELFAST**	**ULM**
N	113	120	109	116
Venue				
Opportunity cost	240.0	440.0	408.7	360.0
Rent cost	26.6	0.0	0.0	0.0
Staff Cost				
Group sessions	625.3	764.2	671.6	937.9
Telephone calls	260.5	416.9	13.9	335.8
Travel costs				
Travel cost (staff)	0.0	55.0	84.7	0.0
Travel cost staff opportunity cost	124.7	31.6	128.5	0.0
Travel cost (participants)	485.9	0.0	1180.1	464.0
Travel cost (participants opportunity cost)	632.8	613.0	309.0	339.1
Equipment				
Equipment	0.0	0.0	0.0	5.0
Other costs				
Other costs	480.0	0.0	224.8	270.0
Total cost (1) excluding opportunity cost	**1878.3**	**1236.1**	**2175.0**	**2012.7**
Cost/participant (1)	**16.6**	**10.3**	**20.0**	**17.4**
Total cost (2) including travel and venue opportunity cost	**2363.3**	**2265.7**	**1756.5**	**2247.8**
Cost/participant (2)	**20.9**	**18.9**	**16.1**	**19.4**

Supplementary Appendix S4: WTP Thresholds

Country	WTP value €	WTP value £
UK	20,433	20,000
UK	30,650	30,000
Spain	27,300	
Denmark	37,700	

Supplementary Appendix S5 Within-Trial sensitivity analysis

Table 1: Sensitivity analysis considering alternative definitions of costs

	Arm			
	ERS+SMS	**ERS**	**Difference**	**ICER** (Incremental Cost/Incremental QALY)
QALY	1.449	1.4323		
Societal cost	12543	12266	**277**	**10375**
Cost falls+social cost	2662	1812	**850**	**31835**
Cost of intervention +20%	3205	3045	**160**	**5993**
Cost of intervention -20%	3138	3069	**69**	**2584**
Opportunity cost of intervention	3295	3137	**158**	**5918**
	Arm			
	ERS+SMS	**UC**	**Difference**	
QALY	1.449	1.4357		
Societal cost	12543	12380	**163**	**12256**
Cost falls+social cost	2662	454	**2208**	**166015**
Cost of intervention +20%	3205	2662	**543**	**40827**
Cost of intervention -20%	3138	2683	**455**	**34211**
Opportunity cost of intervention	3295	2603	**692**	**52030**

Table 2: Sensitivity analysis considering the one country approach to evaluate costs and outcomes

Results table: within trial cost, QALY, Capability QALY and ICER One-country approach				
	Arm			
	ERS+SMS	**ERS**	**Difference**	**ICER (€)**
Cost	4802	4859	**-57**	
QALY	1.3737	1.3429	**0.0308**	**SMS+ERS dominates**
YFC	1.498	1.4826	**0.0154**	**SMS+ERS dominates**
	ERS+SMS	**UC**	**Difference**	
Cost	4802	4339	**463**	
QALY	1.3737	1.3616	**0.0121**	**38264**
YFC	1.498	1.4921	**0.0059**	**78475**

Table 3: Sensitivity analysis considering departure from the MAR assumption: MNAR scenarios

Results table: MNAR scenarios					
		ICER QALY (€)		ICER CQALY (€)	
Scenario		SMS+ERS VS ERS	SMS+ERS VS UC	SMS+ERS VS ERS	SMS+ERS VS UC
0	baseline	3535	ICER>£30K	9973	ICER>£30K
1	Missing costs and qaly/cap qaly are 10% lower in all arms	3764	18446	10195	ICER>£30K
2	Missing costs and qaly/cap qaly are 10% higher in all arms	3335	ICER>£30K	9641	SMS+ERS dominated
3	Missing costs and qaly/cap qaly are 10% higher in the SMS arm	2797	10556	3745	13432
4	Missing costs and qaly/cap qaly are 10% lower in the SMS arm	SMS+ERS dominated	SMS+ERS dominated	SMS+ERS dominated	SMS+ERS dominated
5	Missing qaly/cap qaly are 10% lower in all arms	3889	17639	10531	ICER>£30K
6	Missing qaly/cap qaly are 10% higher in all arms	3224	ICER>£30K	9319	SMS+ERS dominated
7	Missing qaly/cap qaly are 10% higher in the SMS arm	1530	8860	2049	11275
8	Missing qaly/cap qaly are 10% lower in the SMS arm	SMS+ERS dominated	SMS+ERS dominated	SMS+ERS dominated	SMS+ERS dominated

Supplementary Appendix S6 Long Term results- Scenario analyses

The following three scenario analyses have been conducted to assess the robustness of results to key assumptions, specifically:

- **<u>Decay of intervention effect (Scenario I)</u>**. Testing the robustness of results to the assumptions which have been made in relation to the persistence of the intervention effect is crucial, in consideration of the potential of the behavioural SMS component to mitigate the lack of long-term commitment which is often associated with PA interventions. For this reason, in Scenario I the transition rate between PA states has been calculated as the rate of transition into a different PA state between baseline and 22 months. This is different from the base-case scenario, where, as explained in Table 3, transitions rates were calculated in the first year considering movements between baseline and post-intervention, while subsequent transitions consider movements between post-intervention and 22 months. In other terms, instead of modelling the decay of the PA levels considering a different transition rate from year 2 on, in Scenario I we consider the average rate, calculated over the entire time span.
- **<u>Comorbidity (Scenario II)</u>** The SITLESS model does not account explicitly for comorbidities, since once in a disease state, participants can only stay in that state or move to death. Therefore, in Scenario II, a utility decrement has been applied to account for the lower utility associated to comorbidities [48]. In this way, besides indirectly accounting for the effect of comorbidities considering age-specific mortality rates, we further consider the reduction in utility associated to the coexistence of two or more diseases. A disutility value of 3.88% (95%CI: −5.37%,-2.39) has been applied; this has been multiplied by the average number of disease of a SITLESS participants
- **<u>Sedentary behaviour</u> (Scenario III)** In Scenario III, a mortality decrement was applied to account for the detrimental effect of SB, i.e. the increase in mortality risk caused by an excessive SB, which may arise regardless of meeting the recommended PA levels [18]. The mortality risk for active and inactive individuals has been adjusted using the hazard ratio of 1.27 estimated by Ekelund et al [18]'.

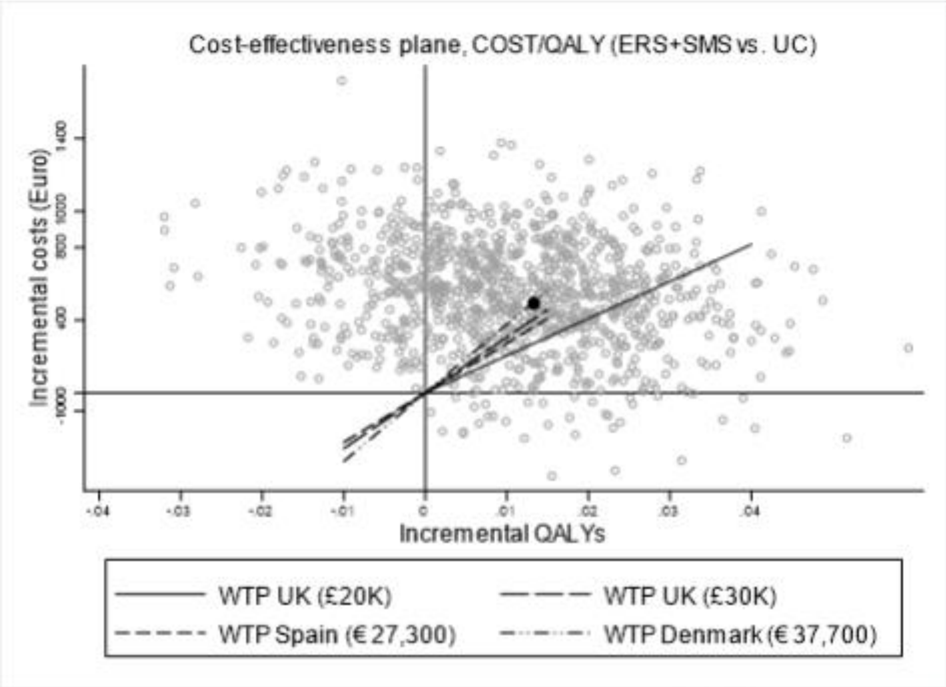
Table 1 below shows the cost-effectiveness results for each of these scenarios, considering the 5 and 15 years time horizon.

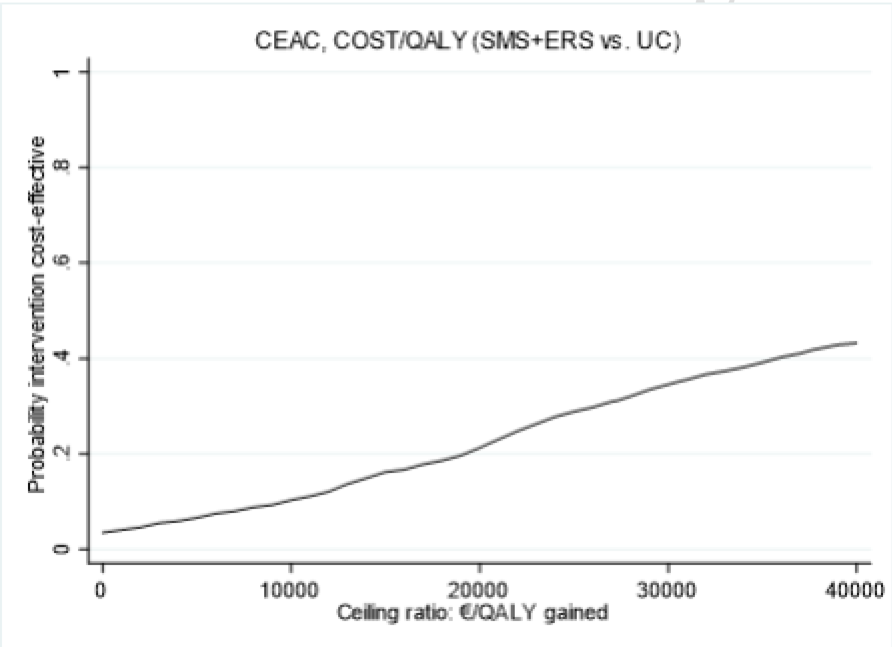
Table 1: Incremental costs, incremental QALY and ICER for the long-term model scenario analyses

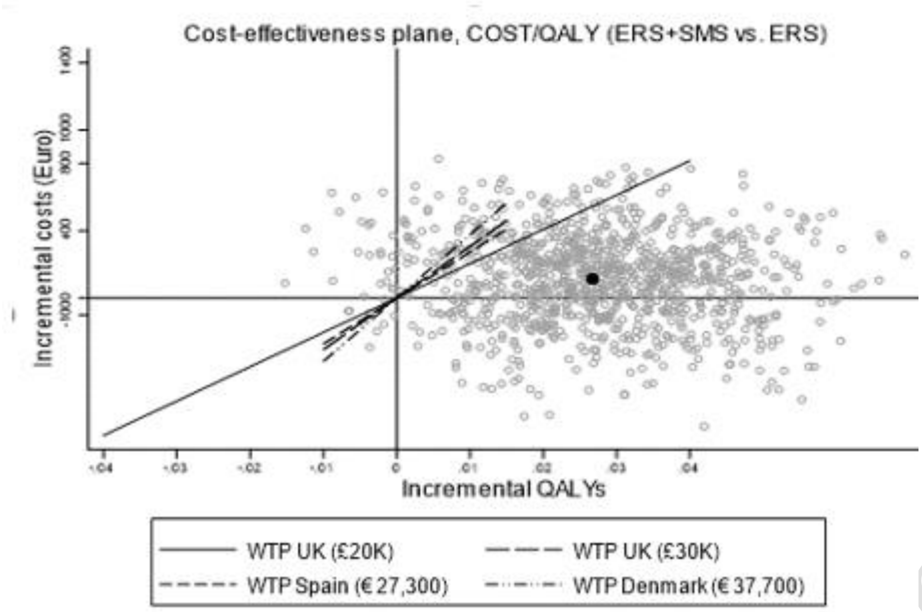
	Arm	Total costs	Total QALYs	Comparison	Incremental costs (CI)	Incremental QALY (CI)	ICER
5 YEARS Time horizon	**SMS+ERS**	13,290	2.6591				
Scenario I	**ERS**	13,250	2.6638	SMS+ERS vs. ERS	40(-57; 151)	-0.0047 (-0.0162; 0.0050)	***SMS+ERS is dominated***
Transition rates calculated over 22 months	**UC**	13,312	2.6566	SMS+ERS vs. UC	-22 (-60:135)	0.0025 (-.00077; 0.0139)	***SMS+ERS dominates***
15 YEARS Time horizon	**SMS+ERS**	45,588	6.9644	SMS+ERS vs. ERS			
Scenario I	**ERS**	45,531	6.9763	SMS+ERS vs. UC	57 (-178; 325)	-0.0119 (-0.0471; 0.0217)	***SMS+ERS is dominated***
Transition rates calculated over 22 months	**UC**	45,583	6.9634	SMS+ERS vs. UC	5 (-286; 250)	0.0010 (-0.0356; 0.0419)	***5075***
5 YEARS Time horizon	**SMS+ERS**	13,294	2.4032				
Scenario II	**ERS**	13,326	2.4012	SMS+ERS vs. ERS	-32 (-140; 57)	0.0020 (-0.0036; 0.0102)	***SMS+ERS dominates***
Comorbidities utility decrement	**UC**	13,347	2.4000	SMS+ERS vs. UC	-52 (-194; 51)	0.0032 (-0.0032; 0.0136)	***SMS+ERS dominates***
15 YEARS Time horizon	**SMS+ERS**	45,634	6.5276				
Scenario II	**ERS**	45,604	6.5285	SMS+ERS vs. ERS	30 (-173; 283)	-0.0008 (-0.0279; 0.0239)	***SMS+ERS is dominated***
Comorbidities utility decrement	**UC**	45,628	6.5252	SMS+ERS vs. UC	6 (-243; 260)	0.0024 (-0.0233; 0.0284)	***2611***

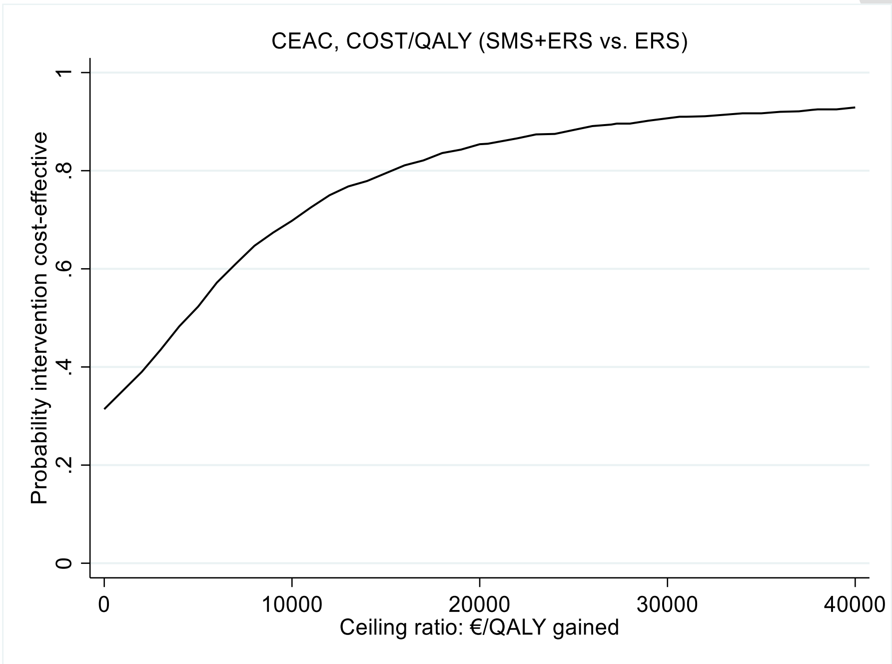
Note: credibility intervals in parenthesis

Supplementary Appendix S7 Cost effectiveness planes and CEACs






Cost-effectiveness plane, COST/QALY (ERS+SMS vs. ERS)
Incremental costs (Euro)
Incremental QALYs
WTP UK (£20K)
WTP UK (£30K)
WTP Spain (€ 27,300)
WTP Denmark (€ 37,700)


CEAC, COST/QALY (SMS+ERS vs. ERS)
Probability intervention cost-effective
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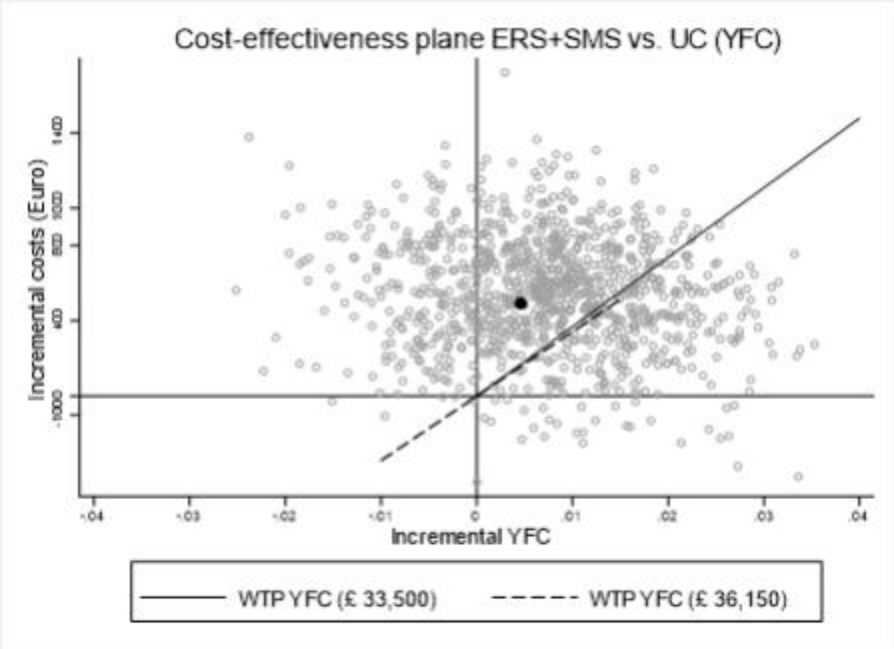
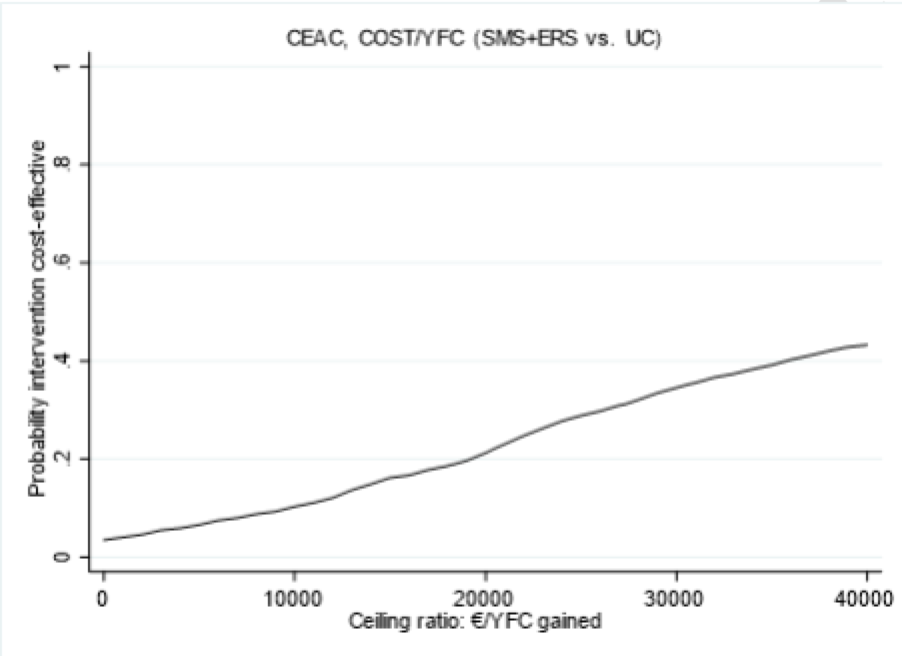
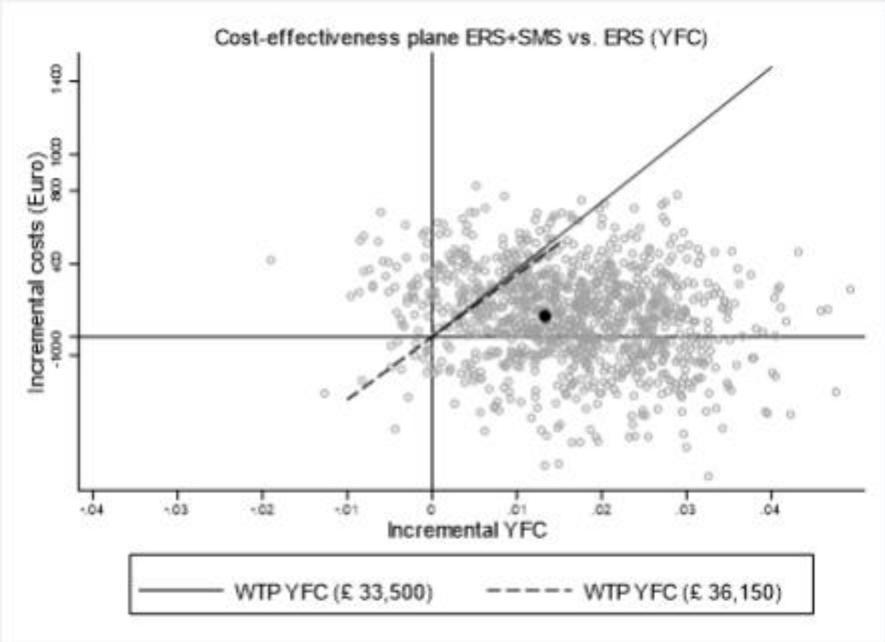
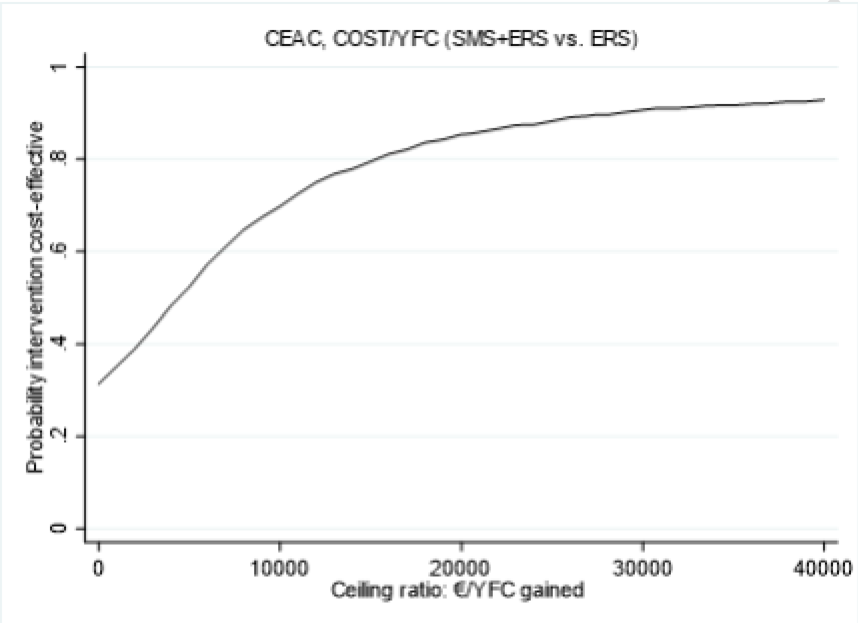
.2
.4
.6
.8
1
0
10000
20000
30000
40000
Ceiling ratio: €/QALY gained


Cost-effectiveness plane ERS+SMS vs. UC (YFC)
Incremental costs (Euro)
Incremental YFC
WTP YFC (£ 33,500)
WTP YFC (£ 36,150)


CEAC, COST/YFC (SMS+ERS vs. UC)
Probability intervention cost-effective
0
.2
.4
.6
.8
1
0
10000
20000
30000
40000
Ceiling ratio: €/YFC gained


Cost-effectiveness plane ERS+SMS vs. ERS (YFC)
Incremental costs (Euro)
Incremental YFC
-.04
-.03
-.02
-.01
0
.01
.02
.03
.04
WTP YFC (£ 33,500)
WTP YFC (£ 36,150)


CEAC, COST/YFC (SMS+ERS vs. ERS)
Probability intervention cost-effective
0
.2
.4
.6
.8
1
0
10000
20000
30000
40000
Ceiling ratio: €/YFC gained

Supplementary Appendix S8: summary statistics

SITLESS primary outcomes

Axis1 CPM			
	Mean	**95% CI**	
ERS+SMS	197.15	186.21	208.09
ERS	198.45	188.85	208.06
UC	192.41	183	201.81
% Sedentary Time			
	Mean	**95% CI**	
ERS+SMS	78.81%	78.11%	79.52%
ERS	78.54%	77.88%	79.21%
UC	79.11	78.49%	79.74%

Baseline variables

	Mean	**Standard deviation**	**Minimum**	**Maximum**
Age at randomisation into SITLESS				
ERS+SMS	75.14	6.16	64	92
ERS	75.19	6.28	65	91
UC	75.48	6.40	64	93
Number of comorbidities				
Control	2.94	2.18	0	10
ERS	2.83	1.97	0	10
SMS+ERS	3.01	2.04	0	16

Gender	**Male**	**Female**		
ERS+SMS	38.20%	61.80%		
ERS	38.30%	61.70%		
UC	38.20%	61.80%		
Marital status	**Single**	**Married/Stable relation**	**Widow/Widower**	**Divorced**
ERS+SMS	9.09%	57.73%	25.91%	12.27%
ERS	8.94%	52.98%	26.83%	11.24%
UC	8.80%	52.55%	28.47%	10.19%

Living arrangements	**Living alone**	**Not living alone**
ERS+SMS	41.32%	58.68%
ERS	38.03%	61.97%

UC	39.96%	60.04%

Education	I do not know how to read and write	I know how to read an write	Primary education	Secondary education	University
ERS+SMS	0.45%	3.34%	20.27%	52.78%	23.16%
ERS	0.46%	2.97%	21.46%	51.83%	23.29%
UC	0.22%	1.79%	20.98%	55.36%	21.65%

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