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Published in:
BMJ Open

Document Version:
Publisher's PDF, also known as Version of record

Queen's University Belfast - Research Portal:
[Link to publication record in Queen's University Belfast Research Portal](#)

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BMJ Open Cost-effectiveness of exercise referral schemes enhanced by self-management strategies to battle sedentary behaviour in older adults: protocol for an economic evaluation alongside the SITLESS three-armed pragmatic randomised controlled trial

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To cite: Deidda M, Coll-Planas L, Giné-Garriga M, *et al*. Cost-effectiveness of exercise referral schemes enhanced by self-management strategies to battle sedentary behaviour in older adults: protocol for an economic evaluation alongside the SITLESS three-armed pragmatic randomised controlled trial. *BMJ Open* 2018;**8**:e022266. doi:10.1136/bmjopen-2018-022266

► Prepublication history and additional material for this paper are available online. To view these files, please visit the journal online (<http://dx.doi.org/10.1136/bmjopen-2018-022266>).

Received 14 February 2018
Revised 22 August 2018
Accepted 30 August 2018



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ABSTRACT

Introduction Promoting physical activity (PA) and reducing sedentary behaviour (SB) may exert beneficial effects on the older adult population, improving behavioural, functional, health and psychosocial outcomes in addition to reducing health, social care and personal costs. This paper describes the planned economic evaluation of SITLESS, a multicountry three-armed pragmatic randomised controlled trial (RCT) which aims to assess the short-term and long-term effectiveness and cost-effectiveness of a complex intervention on SB and PA in community-dwelling older adults, based on exercise referral schemes enhanced by a group intervention providing self-management strategies to encourage lifestyle change.

Methods and analysis A within-trial economic evaluation and long-term model from both a National Health Service/personal social services perspective and a broader societal perspective will be undertaken alongside the SITLESS multinational RCT. Healthcare costs (hospitalisations, accident and emergency visits, appointment with health professionals) and social care costs (eg, community care) will be included in the economic evaluation. For the cost-utility analysis, quality-adjusted life-years will be measured using the EQ-5D-5L and capability well-being measured using the ICEpop CAPability measure for Older people (ICECAP-O) questionnaire. Other effectiveness outcomes (health related, behavioural, functional) will be incorporated into a cost-effectiveness analysis and cost-consequence analysis. The multinational nature of this RCT implies a hierarchical structure of the data and unobserved heterogeneity between clusters that needs to be adequately modelled with appropriate statistical and econometric techniques. In addition, a long-term population health economic model will be developed and will synthesise and extrapolate within-trial data with additional data extracted from the literature linking PA and SB outcomes

Strengths and limitations of this study

- First economic evaluation of a complex, public health intervention to improve health and capability outcomes of community-dwelling, insufficiently active older adults.
- Economic evaluation in a multicountry setting hence requires appropriate sensitivity of results to the costing methodology and the econometric approach to deal with cross-country heterogeneity.
- The protocol will provide useful guidance to design the economic evaluation of a complex public health intervention in multicountry settings.
- Economic evaluation will be reported incorporating a broad set of preference-based health and capability outcomes as well as effectiveness outcomes using cost-utility, cost-effectiveness and cost-consequence analysis.
- While considering sedentary behaviour (SB) alongside physical activity (PA) represents a strength over existing literature, long-term modelling will need to rely on assumptions to combine PA and SB and validation of this may not be possible until further evidence emerges.

with longer term health states. Methods guidance for population health economic evaluation will be adopted including the use of a long-time horizon, 1.5% discount rate for costs and benefits, cost consequence analysis framework and a multisector perspective.

Ethics and dissemination The study design was approved by the ethics and research committee of each intervention site: the Ethics and Research Committee of Ramon Llull University (reference number: 1314001P) (Fundació

Blanquerna, Spain), the Regional Committees on Health Research Ethics for Southern Denmark (reference number: S-20150186) (University of Southern Denmark, Denmark), Office for Research Ethics Committees in Northern Ireland (ORECNI reference number: 16/NI/0185) (Queen's University of Belfast) and the Ethical Review Board of Ulm University (reference number: 354/15) (Ulm, Germany). Participation is voluntary and all participants will be asked to sign informed consent before the start of the study. This project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement number 634270. This article reflects only the authors' view and the Commission is not responsible for any use that may be made of the information it contains. The findings of the study will be disseminated to different target groups (academia, policymakers, end users) through different means following the national ethical guidelines and the dissemination regulation of the Horizon 2020 funding agency. Use of the EuroQol was registered with the EuroQol Group in 2016. Use of the ICECAP-O was registered with the University of Birmingham in March 2017.

Trial registration number NCT02629666; Pre-results.

INTRODUCTION

Economics of inactivity and sedentary behaviour

An insufficient level of physical activity and prolonged sedentary behaviour (PA and SB, respectively, henceforth) is associated with an increased risk of developing major diseases (eg, breast and colon cancers, type 2 diabetes, obesity and depression). Particularly, in the last decade, growing evidence indicates that excessive sitting time may be harmful to health, independent of meeting the recommended PA guidelines.¹

PA and SB represent large costs to the healthcare system and society more broadly. In England, the cost of physical inactivity among the general population (direct costs related to chronic diseases and indirect costs related to the loss of productivity associated to mood and anxiety disorders) has been estimated to be £8.3 billion per year² whereas in Europe that estimate equated €80.4 billion in 2012 (6.2% of total healthcare expenditure across the EU-28). In this regard, reducing inactivity by 20% among the adult population would result in a cost-saving of €16.1 billion.³

The burden of an inactive lifestyle is predicted to be increasing for older adults, which represent the fastest growing segment of the world population,⁴ accounting for 30%–40% of total healthcare spending across Europe.⁵

An increase in the percentage of the total population who are older adults will be accompanied by an increase in the incidence of diseases associated with old age such as cardiovascular disease, cancer, type 2 diabetes, accidental falls, obesity, metabolic syndrome, mental disorders and musculoskeletal diseases.⁶ Furthermore, the frailty associated with old age constitutes an additional risk factor for adverse health outcomes (falls, hospitalisation, disability and death).⁷ Maintaining or engaging in a physically active lifestyle and reducing SB may result in attenuating cognitive and functional decline over time, alleviating the symptoms of various chronic conditions associated to old age⁸ and preventing or even reversing frailty.^{9 10}

More broadly, an active lifestyle has the potential to increase the elderly well-being, in line with the concept of 'active aging' and with the aim to 'extend healthy life expectancy and quality of life for all people as they age, including those who are frail, disabled and in need of care'.¹¹

The substantial economic impact of an inactive lifestyle justifies the need for a robust health economic evaluation to report the cost-effectiveness of interventions to promote active lifestyles to reduce the likelihood of developing diseases and disability associated with old age and preventing them.

Interventions to reduce SB or a lack of PA: economic evaluation evidence

Evidence regarding the cost-effectiveness of public health interventions directed towards the increase of PA and reduction of SB is typically characterised by a substantial heterogeneity regarding the type of implemented intervention and the target population.^{12 13} Most studies analyse the effect of interventions on healthy populations^{14 15} or to a population with specific chronic conditions.^{16–18} Only few focus on older adults,^{19–21} without major health conditions,^{20 21} with specific chronic conditions^{19 22 23} or mobility problems.^{24 25}

A review carried out by Owen *et al*²⁶ pointed out that most exercise referral scheme (ERS) interventions (among a list of the UK's National Institute for Health and Care Excellence (NICE) public health interventions) were under the UK's £20 000 cost per quality-adjusted life-year (QALY) threshold, thus representing a cost-effective use of resources. However, studies usually compare ERS with usual care (UC), and evidence is limited or plagued by significant uncertainty around estimates of cost-effectiveness.²⁷ Garrett *et al*¹³ reported the results of a systematic review of community-based interventions directed towards the improvement of PA, finding that most interventions, especially those not requiring direct supervision, were cost-effective.²³ Pavey *et al*¹⁴ found that ERS interventions were cost-effective only in inactive but healthy populations.¹⁰ de Vries *et al*²⁴ evaluated the cost-effectiveness of a patient-centred physical therapy strategy with tailored motivational and coaching sessions and physical training directed towards individuals over 70 years old with mobility problems; they found that the intervention was effective in increasing PA and reducing frailty and provided good value for money.²⁰

Poor adherence and lack of long-term commitment have been identified as the main challenges of ERS interventions, thus suggesting scope for behavioural interventions.^{12 14} However, only few studies evaluate such interventions.^{16 21} Furthermore, there is a lack of evidence regarding the long-term effectiveness and cost-effectiveness of interventions to increase PA and reduce SB.¹⁴

The SITLESS intervention

The SITLESS study is a multinational, multicentre, three-armed randomised controlled trial (RCT)

investigating the short-term and long-term cost-effectiveness of a complex intervention to increase PA and reduce SB in older adults from four European countries. The cost-effectiveness of a joint intervention of ERS and self-management strategies (SMS) will be evaluated compared with two alternatives: ERS alone and usual care (UC). Full details of the RCT protocol are reported elsewhere.²⁸

ERS have become one of the most widely used instruments to promote PA.^{14 29} In an ERS intervention, individuals—usually insufficiently active or affected by specific diseases which might benefit from PA—are assigned to a primary care or to an exercise facility (usually in the community setting), which design and monitor a tailored exercise programme. However, ERS are not usually focused on reducing SB^{20 30–32} and evidence of ERS effectiveness typically relates to the short-term as well as to specific subgroups of individuals (eg, overweight adults, or individuals who are already slightly active³³) hence they are often not generalisable to the older population. Furthermore, evidence regarding the effectiveness and cost-effectiveness of ERS compared with alternative interventions (eg, standard advice) is limited.^{29 34}

Individual commitment towards PA and reduction of SB are driven by behavioural, demographic and socioeconomic (possibly country-specific) factors.^{35 36} Given this, the behavioural intervention in the form of SMS could modify individual behaviour more effectively than ERS or UC.³⁷ Furthermore, SMS might exert an incremental benefit—in terms of increased PA and reduction of SB—with respect to ERS alone, in terms of enhanced motivation to sustain the behaviour change over the long term, thus overcoming problems related to the limited uptake and low adherence to the programme which are usually associated with ERS.^{18 19}

The SITLESS RCT enhances the PA intervention with an SMS intervention based on behavioural change techniques, encompassing a range of components: behavioural goal setting, self-monitoring of progress and social support among peers and the existing network, external monitoring, problem solving, environmental signposting. The SMS intervention targets PA and SB with distinct, through related, techniques.²⁸

This paper describes the protocol for the economic evaluation alongside the SITLESS RCT. The aim is to determine whether enhancing ERS by SMS is a cost-effective strategy and provides good value for money. In addition, this economic evaluation protocol will outline the additional challenges posed by the multicountry nature of the study, describing the proposed methodologies to deal with the identification, measurement and valuation of costs and outcomes. The health economics logic model (online supplementary appendix 1) illustrates the linkage between the resources used and the outcomes of interest related to the SITLESS intervention.

METHODS

Design

Following good practice for the design of economic evaluations alongside RCTs,³⁸ data collection instruments were designed in collaboration with the trial team to collect information on the cost of the ERS and SMS intervention, resources used by patients (eg, usage of medical, social and community services) and preference-based quality of life (QOL) and capability outcomes, at baseline and over the trial follow-up (12 and 18 months after intervention) considering a health and social service perspective and a broader social perspective. While the SITLESS complex intervention is standardised, the data collection instruments were tailored to each country context (eg, inclusion of country-specific examples of community/social services).

The economic evaluation will follow the UK's most recent guidance for the economic evaluation of public health interventions NICE,³⁹ as well as Consolidated Health Economic Evaluation Reporting Standards (CHEERS) guidelines for reporting results.⁴⁰

Study population

The target population is community-dwelling older adults who fulfil the following criteria: aged 65 or above; able to walk independently for at least 2 min; have no major physical limitations (ie, obtaining <4 in the Short Physical Performance Battery); and who are insufficiently active (perform regular PA) for at least 30 min 5 or more days of the week. All individuals will be recruited according to country-specific primary prevention pathways. Overall, according to the sample size estimation, 1338 individuals will be recruited for the trial (446 per group).

Setting and location

The SITLESS trial is a multicountry, multicentre trial. The intervention will be delivered in primary care or community settings in four sites: Barcelona (Spain), Odense (Denmark), Ulm (Germany) and Belfast (UK).

A multicountry RCT has benefits in terms of higher statistical power and generalisability of the economic results.^{41 42} However, the multinational nature of SITLESS occasions substantial cross-country heterogeneity in terms of: demographic structure (ie, morbidity and mortality patterns, ageing structure); differences in healthcare systems (eg, payment systems, health provider incentives); differing unit cost sources; differing availability of healthcare services and clinical practices⁴³; individual attitudes towards PA (personal motivation, health and mobility issues, genetic factors); and social and physical environments or cultural differences in behaviour and preferences of participants (eg, local opportunities to do PA, social gathering, etc).

For all the reasons mentioned above, identifying and accounting for cross-country heterogeneity is a key issue for the economic evaluation of SITLESS.

Intervention and comparator

The cost-effectiveness of a joint intervention of ERS and SMS will be compared (18 months) with two control groups: (1) ERS alone; (2) UC (ie, written general booklet standardised across sites, including the WHO recommendation regarding PA regular practice for health, and two sessions on healthy ageing regarding fall prevention and healthy nutrition).

Patient and public involvement

SITLESS, as a Responsible Research and Innovation project, has created guidance for the involvement of several stakeholders in the project from the onset. They comprise older adults of both genders, representatives of older adults' associations, primary healthcare and sports professionals, policymakers and other local stakeholders of relevance (eg, health insurance, where relevant). Accordingly, four local advisory boards were created at the beginning of the project, one on each intervention site (Barcelona, Odense, Belfast, Ulm), and were periodically involved in the study from its onset. The development of the research question and outcome measures were shared with each advisory board and therefore informed according to patients' priorities and motivations, experience and preferences. We also did a literature review that included how older adults perceive PA and SB, and how could we achieve sustained changes of behaviour to enhance health.

The involvement of stakeholders as primary, secondary and tertiary end users in the design of the study was specifically in the intervention design. We explored experiences, preferences and priorities of older adults regarding behaviour change through focus groups that were convened thanks to the older people organisations belonging to the local advisory boards. We took into account their contributions at each site, and the main results were included in the intervention design.

Local advisory boards also discussed and provided their contributions to the challenges faced regarding recruitment, retention of participants in the study and the dissemination strategies.

Qualitative interviews were conducted with a purposeful sample of participants in each intervention site and from each arm of the trial to explore their perceptions on the intervention.

Once the trial ends, we are planning on disseminating the results at each primary care centre and local leisure centres to end users, health professionals and relevant stakeholders. We would like to share our results to Citizen Science events, also involving participants of each site.

Study perspective

The economic evaluation will be conducted from a health service and personal social services perspective as recommended by UK's NICE guidelines.³⁹ To this end, health and non-health care costs (and cost savings) incurred by both the provider and the participant will be considered.

According to NICE guidelines, which suggest emphasising overall welfare, rather than health per se, a cost-effectiveness analysis (CEA) from a personal social services perspective and a cost-consequence analysis (CCA) adopting a broader societal perspective may be performed as well.

Time horizon

The assessment of the primary within-trial economic analysis will be conducted at baseline, after intervention, and at 12 and 18 months' follow-up. The economic evaluation includes a long-term model to extrapolate the cost-effectiveness results beyond the 18 months within trial component.

Discount rate

Following UK's NICE public health economic evaluation guidelines,³⁹ a discount rate of 1.5% will be employed and sensitivity analysis will explore the impacts of rates of 3.5% and 6%.

Measures of outcome

The measures of outcome employed in the economic evaluation and the timing of their collection are presented in [table 1](#). While QALYs are the main outcome measure to be used in a cost-utility analysis (CUA) framework, CEA and CCA will make use of the broader set of outcomes collected within trial.

QALYs will be estimated using the EQ-5D-5L⁴⁴ and capability well-being estimated using the ICEpop Capability Measure for Older People (ICECAP-O).⁴⁵ Outcomes will be assessed at baseline, month 4 (end of ERS intervention), month 16 (12 months after intervention) and month 22 (18 months after intervention) allowing estimation of the area under the curve (AUC). The EQ-5D-5L focuses on health attributes while the ICECAP-O instrument will assess capability well-being (according to Sen's capability theory⁴⁶), thus incorporating both health and non-health dimensions.⁴⁷

QOL: EQ-5D-5L

The EQ-5D-5L questionnaire measures health-related quality of life (HRQOL) in terms of five dimensions (mobility, self-care, daily activities, pain and discomfort, anxiety and depression) in a 1–5 scale. It also includes a visual analogue scale on which patients rate their own health between 0 (best imaginable health state) and 100 (worst imaginable health state). Assigning weights to each response of the five dimensions, it is possible to generate a synthetic index that will summarise the HRQOL at the individual level. The EQ-5D has been used by several studies examining the cost-effectiveness of ERS as a measure of HRQOL.^{17 19 48}

EQ-5D utility scores will be derived using UK tariffs. In consideration of the multinational aspect of the analysis, the quality adjustment weights for each health state at different periods should be obtained by using country-specific EQ-5D tariffs, which reflect country-specific differences in health perceptions and preferences and

Table 1 Overview of outcome measures

Measure	Means of collection	Timing of collection
QALYs		
Quality of life (EQ-5D)	Self-reported	Baseline (T0), month 4 (end of ERS intervention)
Capability in older people (ICECAP-O)	Self-reported	(T1), month 16 (12 months after intervention) (T2) and month 22 (18 months after intervention) (T3)
Primary outcomes		
SB (measured as sitting time)	Face-to-face interview	Baseline (T0), month 4 (end of ERS intervention)
PA (measured as daily counts/min and daily step counts)	Face-to-face interview	(T1), month 16 (12 months after intervention) (T2) and month 22 (18 months after intervention) (T3)
Secondary outcomes		
Physical function	Face-to-face interview	
Muscle function	Face-to-face interview	
Anthropometry	Face-to-face interview	
Bioimpedance	Face-to-face interview	
Blood pressure	Face-to-face interview	
Activities of daily living	Self-reported	
Self-rated health and health-related quality of life	Self-reported	
Anxiety	Self-reported	Baseline (T0), month 4 (end of ERS intervention)
Depressive symptoms	Self-reported	(T1), month 16 (12 months after intervention) (T2) and month 22 (18 months after intervention) (T3)
Social network	Self-reported	
Physical activity self-regulation	Face-to-face interview	
Self-efficacy for exercise	Face-to-face interview	
Disability	Face-to-face interview	
Fear of falling	Face-to-face interview	
Loneliness	Self-reported	
Executive function	Face-to-face interview	
Physical fatigue ⁷²	Face-to-face interview	

ERS, exercise referral scheme; ICECAP-O, ICEpop Capability Measure for Older People; PA, physical activity; QALY, quality-adjusted life-years; SB, sedentary behaviour.

might significantly affect CUA.^{49–51} However, so far country-specific sets of tariffs for the EQ-5D-5L have not been directly elicited in any of the SITLESS countries with a validated procedure (value sets for England only are available) and in line with a recent NICE position statement,⁵² we will make use of the ‘crosswalk’ procedure, developed by the EuroQol Group to link the EQ-5D-5L and EQ-5D-3L. Crosswalk value sets for the EQ-5D-5L are currently available for all the countries participating in the SITLESS study.⁵³

The utility value derived from the EQ-5D-5L questionnaire will be used to derive QALYs using standard AUC methods, eventually adjusted for group-specific differences in baseline utility.⁵⁴

ICEpop Capability Measure for Older People

The ICECAP-O instrument measures capability well-being across five capability dimensions (attachment, security, role, enjoyment, control). English, Spanish and German translations were available for ICECAP-O; however, the questionnaire was translated for the first time in Danish

for the SITLESS trial. Given that country-specific tariffs are not available for all the countries in the SITLESS trial, the ICECAP-O utility scores were derived using UK tariffs.

Resource use

Identification and measurement of resource use

The costs of delivering and administering the SITLESS intervention and the control will be identified and measured alongside potential cost impacts, thus taking into account both costs incurred as well as cost savings arising across arms.

In line with the National Health Service and personal social services perspective, two sources of costing have been taken into account. First, the costs borne by the primary care/exercise facility to deliver the SITLESS intervention and the control are considered. The SMS intervention is tailored to each individual, thus requiring the collection of individual-specific costs (eg, duration of the contact, staff present, transport costs sustained by staff and participants) using the SMS intervention cost log. Average costs (eg, equipment used during the SMS

sessions; refreshments) which are not likely to change across individuals will also be identified and measured. Unlike the SMS, the delivery of the ERS and UC interventions are entirely standardised. Thus, the associated cost can be regarded as uniform and not as an individual-specific cost. Therefore, the data collection instruments (ERS and UC cost logs) aim to capture the average cost sustained when delivering these interventions. Specifically, the ERS cost log identifies and measures: the number and type of staff involved in delivering the intervention; travel costs sustained by participant and staff; average cost of the equipment used, considering the number of equipment used, typical lifespan and cost. A sample of the data collection instruments can be provided on request.

Besides the cost of the intervention, a wide range of resource use, including use of exercise facilities as well as use of health and social services (table 2), will be derived through a bottom-up exercise, following similar studies^{14 17} and collected through a questionnaire.

Research costs including the cost of the ActiGraph, ActivPal and Axivity accelerometers—used to measure PA and SB—will not be included. However, research costs related to the recruitment of participants will be identified and reported (separate from the economic evaluation) to provide likely implementation costs should the trial be rolled out in future.

Valuation of resource use

Evaluating costs in multinational trials requires handling a non-negligible amount of between-country heterogeneity that needs to be tackled appropriately in order to allow for comparability.

Unit prices need to be converted into a common currency (€) by use of purchasing power parity statistics reported by the Organisation for Economic Co-operation and Development for a base year to allow proper comparison.⁴¹ Furthermore, following a multicountry costing approach, unit cost estimates from each country will be used to evaluate the resources used in these countries but sensitivity analysis using UK unit prices will be performed as well. Indeed, while systematic reviews provide mixed evidence on the most used costing method,^{55–57} using country-specific unit costs is a common and recommended practice to evaluate resources in multinational RCTs.^{58 59} However, recent ISPOR guidelines cast doubts on the superiority of the multicountry approach,⁵⁸ arguing that a multicountry costing may not be an effective strategy to adjust for cross-country heterogeneity.

An overview of resource use and cost measures to be employed in the economic evaluation is presented in table 2, while online supplementary appendix 2 provides a summary of the unit cost sources that will be used to value resource use.

Sample size

The estimated sample size to assess overall effectiveness of the intervention in the clinical trial is 1338 subjects (distributed in three intervention groups of 446 participants).²⁸

This sample size will ensure that it is possible to detect a clinically relevant increase of 30 daily counts per minute (CPM) between the ERS-SMS and the control groups or between the ERS-SMS and the ERS groups.

This sample has been estimated in a two-sided test, at a power of 80% and an α of 0.05, a common SD of 139 of the mean and a 24% dropout rate. A change of 30 CPM is considered a measurable moderate effect size in this population, assessed with ActiGraph GT3X+, and 139 is the SD for CPM found in the literature.⁶⁰

Within-trial economic analysis

The within-trial economic analysis will establish the expected cost-effectiveness of SMS+ERS compared with ERS alone and UC through a number of different analyses. The main within-trial analysis will be reported using a CUA framework, which will calculate the incremental cost per QALY (calculated using EQ-5D). Further reporting will include the incremental cost per year of full capability (calculated using the ICECAP-O) of the SITLESS intervention versus both the control groups. In addition, the cost per unit of increased PA or reduction in SB will be calculated using a cost-effectiveness framework.

Furthermore, a CCA framework will be also implemented. Given the complex nature of the SITLESS intervention, it is likely that all the relevant benefits of the intervention will not be captured by a single utility measure or a single outcome measure. To this end, the CCA framework would facilitate the presentation of a wider battery of outcomes collected within the SITLESS trial. Table 3 shows the health economics framework (CUA, CBA or CCA), and the related outcome measures, perspectives and format for presenting results.

Statistical analysis

The multicountry nature of the SITLESS intervention implies that cost and outcome data fall naturally in a hierarchical structure, meaning that multiple ‘micro-units’ (individuals) are nested within multiple macrounits (countries).^{41 61} Dealing with this hierarchical data structure will be an important consideration for the economic evaluation analysis, and will allow appropriate modelling of within and between-country variability as well as the clustering effect of the intervention itself.^{62 63} However, if no significant degree of country-level clustering is found in the SITLESS data, the estimation will rely on widely used non-hierarchical models (eg, a pooled model with country fixed effects⁵⁷).

An exploratory analysis will reveal country patterns in cost and effectiveness, as well as highlighting the presence of outliers that—due to the small number of countries—may have a stronger impact on economic results.

Addressing uncertainty

Deterministic and stochastic sensitivity analysis will be performed to measure uncertainty around parameters considered to be influencing the cost-effectiveness of the SITLESS intervention.

Table 2 Overview of cost measures

ERS; usual care; ERS+SMS	ERS; usual care	Cost component	Timing of collection	Source of data	Multicountry-specific issues
		Use of exercise services Visits to exercise facilities	Baseline (T0), month 4 (end of ERS intervention) (T1), month 16 (12 months postintervention) (T2) and month 22 (18 months postintervention) (T3)	Patient Resource Use Questionnaire	
		Opportunity cost of walking/exercise	Baseline (T0), month 4 (end of ERS intervention) (T1), month 16 (12 months postintervention) (T2) and month 22 (18 months postintervention) (T3)	Patient Resource Use Questionnaire	
		Community costs (use of social services)	Baseline (T0), month 4 (end of ERS intervention) (T1), month 16 (12 months postintervention) (T2) and month 22 (18 months postintervention) (T3)	Patient Resource Use Questionnaire	Use of country-specific examples
		National health system costs (use of health services) Visits (eg, GP, nurses, physiotherapist)	Baseline (T0), month 4 (end of ERS intervention) (T1), month 16 (12 months postintervention) (T2) and month 22 (18 months postintervention) (T3)	Patient Resource Use Questionnaire	Specify if covered by national health system; private insurance; copayment; herself/himself
		Overnight hospital stays	Baseline (T0), month 4 (end of ERS intervention) (T1), month 16 (12 months postintervention) (T2) and month 22 (18 months postintervention) (T3)	Patient Resource Use Questionnaire	
		Medication (prescribed and non-prescribed)	Baseline (T0), month 4 (end of ERS intervention) (T1), month 16 (12 months postintervention) (T2) and month 22 (18 months postintervention) (T3)	Patient Resource Use Questionnaire	Specify if medication is provided free of charge; reduced charge/copayment; regular price
		Opportunity costs—time spent by family members/friends in providing care	Baseline (T0), month 4 (end of ERS intervention) (T1), month 16 (12 months postintervention) (T2) and month 22 (18 months postintervention) (T3)	Patient Resource Use Questionnaire	
		Personal costs related to improvement of health/reduction of sedentary behaviour	Baseline (T0), month 4 (end of ERS intervention) (T1), month 16 (12 months postintervention) (T2) and month 22 (18 months postintervention) (T3)	Patient Resource Use Questionnaire	
		Costs related to falls (falls requiring medical care/hospital admission)	Baseline (T0), month 4 (end of ERS intervention) (T1), month 16 (12 months postintervention) (T2) and month 22 (18 months postintervention) (T3)	Patient Resource Use Questionnaire	
		ERS/UC delivery cost	Only once (average cost)	ERS and UC intervention cost log	
		Primary care/community (SMS service delivery costs)	Every time an SMS session is completed	SMS intervention cost log	

ERS, exercise referral scheme; GP, general practitioner; SMS, self-management strategies; UC, usual care.

Table 3 Overview of Health Economics frameworks, outcome measures, perspective and format for presenting results

Health economics framework	Outcome measure	Perspective	Format for presenting results
Cost-utility analysis (CUA)	EQ-5D	Health and personal social services	Incremental cost/QALY
Cost-capability well-being analysis	ICECAP-O	Health and personal social services	Incremental cost/year in full capability
Cost-effectiveness analysis (CEA)	Sitting time	Health and personal social services	Incremental cost/unit of reduction in sitting time
	Physical activity	Health and personal social services	Incremental cost /10% of daily step count increase
	<i>+ utility measures used in the CUA, as above</i>		
Cost consequence analysis (CCA)	Incremental cost of the SMS+ERS intervention versus comparator, to be compared with the change in secondary outcome (eg, physical function, muscle function, anxiety, disability fear of falling)	Societal	Cost/change in multiple outcomes, for example, change in physical function; change in muscle function; change in QALY/years in full capability; change in daily step counts
	<i>+ utility measures used in the CUA and effectiveness measures used in the CEA, as above</i>		

ERS, exercise referral scheme; ICECAP-O, ICEpop Capability Measure for Older People; QALY, quality-adjusted life-years; SMS, self-management strategies.

Deterministic, one-way sensitivity analysis will examine the impact that changes in the discount rate, unit costs and utility weights would have on the main economic evaluation results. The impact of assumptions regarding resource use and outcome valuation in a multicountry setting will also be explored, including: (A) multicountry/one-country (UK unit costs) costing approach; (B) country-specific utility weights derived through the 'cross-walk' procedure/UK-based EQ-5D. When appropriate, a tornado diagram may be used to explore the effect of a percentage change in each of the key model parameters on the main outcome.

A two-way sensitivity analysis will explore the joint variation of cost and utility weights around a range identified by the one-country and multicountry scenario, and will assess how the incremental cost-effectiveness ratio (ICER) changes in the 'extreme' cases. In addition, sensitivity to the econometric specification used to model cross-country data clustering will be examined and taken into account. Further sensitivity analysis might be required depending on the distributional assumptions regarding cost and outcomes, as well as regarding the presence of outliers.

Probabilistic sensitivity analysis (PSA) around the longer term estimates of costs, effects and cost-effectiveness of the ERS+SMS intervention versus ERS alone and UC will be performed using a 1000 iteration Monte Carlo simulation. PSA has the advantage of indicating the probability of a technology being cost-effective at various thresholds of willingness to pay (WTP). A high probability of being cost-effective should lead to a more positive outcome in a

technology appraisal, whereas the opposite should apply for a low probability.⁶⁴ Using Monte Carlo simulation, a bootstrapped distribution of costs and QALY will be generated and incremental costs and QALY will be shown in a cost-effectiveness plane. Cost-effectiveness acceptability curves will graphically represent the probability that the intervention is cost-effective compared with the controls across a range of cost-effectiveness thresholds. Representing the uncertainty of ICER across a range of WTP is a key issue in the economic evaluation of the SITLESS intervention, given that the WTP is likely to be country specific, reflecting a country's opportunity cost of undertaking the intervention.⁶⁵

Missing data

Following best practice,^{58 66 67} a multiple imputation procedure using chained equations will be used to impute missing data separately for each arm of the trial and predictive mean matching will allow dealing with non-normality of cost and outcome data.⁶⁸ The procedure to deal with missing data will take into account additional, SITLESS-specific, reasons for missingness related to the fact that motivations and barriers for providing information might be age related (eg, physical or cognitive weakness). Furthermore, an analysis of missing data by country will be performed in order to identify any country-specific pattern in the probability of missingness.

Extrapolation beyond trial: lifetime cost-effectiveness

If evidence of differences between the treatment arms in terms of effectiveness, costs or cost-effectiveness is found

in the trial, an extrapolation of the within-trial results to the long term will be performed following NICE³⁹ guidelines. As noted by Pavey *et al*,¹⁴ the long-term effect of an increase in PA levels on health gains is not clear, and it might be difficult to extrapolate the results beyond the observed data. A behavioural Markov model, akin to the model developed by Frew *et al*⁶⁹ and Roux *et al*,⁷⁰ projecting changes in PA behaviour to health outcomes and costs are natural candidates to model the cost-effectiveness of SITLESS in the long term. However, the model will be customised to take specific challenges into account, including: (A) inclusion of SB, using available evidence to ‘convert’ SB into PA (eg, Ekelund *et al*⁷¹); (B) identification of ageing-specific health outcomes; and (C) choice of appropriate time horizon, taking into consideration the target population’s life expectancy. Uncertainty around the longer term estimates of costs, effects and cost-effectiveness of the ERS+SMS intervention versus the comparators will be performed using Monte Carlo simulation techniques. An annual discount rate of 1.5% will be applied to costs and effects in line with NICE guidelines.³⁹

DISCUSSION

The economic evaluation of the SITLESS intervention has been designed to respond to the need to fully evaluate a complex intervention on PA and SB in older adults. The economic implications of PA and SB are magnified for older adults, and may result in a greater use of healthcare resources, leading to a burden of cost for national health systems and society. Furthermore, behavioural interventions such as the SMS implemented in the SITLESS intervention are suited to addressing matters of long-term adherence to the programme, while more standard interventions have been limited by being effective only in the short term.^{12 14 27}

While previous clinical studies have assessed the clinical effectiveness of interventions on PA and SB, cost-effectiveness has not often been assessed. On the other hand, existing studies refer to interventions implemented in a specific context, while, to the best of our knowledge, this is the first RCT which focuses on older adults and takes the multicountry setting into account.

The multicountry nature of the study poses additional methodological challenges for the economic analysis. However, a multinational RCT has the potential to increase the generalisability of the results, thus providing the policymaker with useful guidelines on the value for money provided by complex interventions such as SITLESS. Furthermore, an appropriate sensitivity analysis in the long-term modelling of intervention effects will provide insights on their sustainability—taking into account intervention costs and adherence to intervention programmes similar to SITLESS that are implemented in a ‘real world’ context.

In addition to dealing with the multicountry aspect of the study, the proposed economic evaluation of SITLESS has accounted for several aspects related to the

complexity of such intervention, including: the existence of multiple, interacting components (PA and behavioural component); number and difficulty of the behaviours required by those delivering the intervention; interdisciplinary team involved; existence of externalities and spillovers (eg, to family and informal carers); and interaction between users and providers and system-wide components. Such a complexity does imply additional challenges for the economic evaluation, such as the need to consider a plethora of outcomes to take the multidisciplinary aspect of the intervention into account and the design of data collection instruments balancing standardisation and country tailoring.

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Acknowledgements The authors thank the members of the SITLESS consortium for their help in developing the economic evaluation protocol, and acknowledge the input of all the investigators to the development of the trial. The authors thank the members of the local advisory boards at each intervention site for their contributions throughout the trial.

Collaborators Members of the SITLESS consortium.

Contributors MD drafted the economic evaluation protocol. EM led the design of the economic evaluation of SITLESS and commented on all versions of the economic evaluation protocol. LCP lead the design of the SITLESS trial. EM, MGG, MGB, MRF, MAT, PC and DR provided comments on earlier version of the manuscript. EM, LCP, MGG, MGB, MRF, MAT, PC DR, ASC, FK, NEB, JJW, MS, MDK and KW commented on the final version.

Funding The SITLESS project had been funded by the European Union programme Horizon 2020 (H2020-Grant 634270).

Disclaimer This article reflects only the authors' view and the Commission is not responsible for any use that may be made of the information it contains.

Competing interests None declared.

Patient consent Not required.

Ethics approval The study design was approved by the ethics and research committee of each intervention site: the Ethics and Research Committee of Ramon Llull University (reference number: 1314001P) (Fundació Blanquerna, Spain), the Regional Committees on Health Research Ethics for Southern Denmark (reference number: S-20150186) (University of Southern Denmark, Denmark), Office for Research Ethics Committees in Northern Ireland (ORECNI reference number: 16/NI/0185) (Queen's University of Belfast) and the Ethical Review Board of Ulm University (reference number: 354/15) (Ulm, Germany). Participation is voluntary and all participants will be asked to sign informed consent before the start of the study. The findings of the study will be disseminated to different target groups (academia, policymakers, end users) through different means following the national ethical guidelines and the dissemination regulation of the Horizon 2020 funding agency.

Provenance and peer review Not commissioned; externally peer reviewed.

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REFERENCES

- Owen N, Healy GN, Matthews CE, *et al*. Too much sitting: the population health science of sedentary behavior. *Exerc Sport Sci Rev* 2010;38:105.
- Beale SJ, Bending MW, Trueman P, *et al*. Should we invest in environmental interventions to encourage physical activity in England? An economic appraisal. *Eur J Public Health* 2012;22:869–73.
- ISCA-CEBR. The economic cost of physical inactivity in Europe. 2015.
- WHO. *Global Health and Ageing*. Geneva, Switzerland: World Health Organisation, US National Institute of Aging, 2011.
- Economic Policy Committee. Budgetary challenges posed by ageing populations. 2001.
- Dishman R, Heath G, Lee I-M. Physical activity epidemiology: human kinetics. 2013.
- Buckinx F, Rolland Y, Reginster JY, *et al*. Burden of frailty in the elderly population: perspectives for a public health challenge. *Arch Public Health* 2015;73:19.
- Kujala UM. Evidence on the effects of exercise therapy in the treatment of chronic disease. *Br J Sports Med* 2009;43:550–5.
- Peterson MJ, Sloane R, Cohen HJ, *et al*. Effect of telephone exercise counseling on frailty in older veterans: project LIFE. *Am J Mens Health* 2007;1:326–34.
- Kenny AM, Boxer RS, Kleppinger A, *et al*. Dehydroepiandrosterone combined with exercise improves muscle strength and physical function in frail older women. *J Am Geriatr Soc* 2010;58:1707–14.
- WHO. Active ageing: a policy framework. 2002.
- Williams NH, Hendry M, France B, *et al*. Effectiveness of exercise-referral schemes to promote physical activity in adults: systematic review. *Br J Gen Pract* 2007;57:979–86.
- Garrett S, Elley CR, Rose SB, *et al*. Are physical activity interventions in primary care and the community cost-effective? A systematic review of the evidence. *Br J Gen Pract* 2011;61:e125–33.
- Pavey TG, Anokye N, Taylor AH, *et al*. The clinical effectiveness and cost-effectiveness of exercise referral schemes: a systematic review and economic evaluation. *Health Technol Assess* 2011;15:1–254.
- Cobiac LJ, Vos T, Barendregt JJ. Cost-effectiveness of interventions to promote physical activity: a modelling study. *PLoS Med* 2009;6:e1000110.
- Pentecost C, Farrand P, Greaves CJ, *et al*. Combining behavioural activation with physical activity promotion for adults with depression: findings of a parallel-group pilot randomised controlled trial (BACpac). *Trials* 2015;16:16.
- Isaacs AJ, Critchley JA, Tai SS, *et al*. Exercise Evaluation Randomised Trial (EXERT): a randomised trial comparing GP referral for leisure centre-based exercise, community-based walking and advice only. *Health Technol Assess* 2007;11:1.
- Murphy SM, Edwards RT, Williams N, *et al*. An evaluation of the effectiveness and cost effectiveness of the National Exercise Referral Scheme in Wales, UK: a randomised controlled trial of a public health policy initiative. *J Epidemiol Community Health* 2012;66:745–53.
- Gusi N, Reyes MC, Gonzalez-Guerrero JL, *et al*. Cost-utility of a walking programme for moderately depressed, obese, or overweight elderly women in primary care: a randomised controlled trial. *BMC Public Health* 2008;8:231.
- Munro J, Brazier J, Davey R, *et al*. Physical activity for the over-65s: could it be a cost-effective exercise for the NHS? *J Public Health Med* 1997;19:397–402.
- Clare L, Hindle JV, Jones IR, *et al*. The AgeWell study of behavior change to promote health and wellbeing in later life: study protocol for a randomized controlled trial. *Trials* 2012;13:115.
- Cochrane T, Davey RC, Matthes Edwards SM. Randomised controlled trial of the cost-effectiveness of water-based therapy for lower limb osteoarthritis. *Health Technol Assess* 2005;9:1–114.
- Hurley MV, Walsh NE, Mitchell HL, *et al*. Economic evaluation of a rehabilitation program integrating exercise, self-management, and active coping strategies for chronic knee pain. *Arthritis Rheum* 2007;57:1220–9.
- de Vries NM, Staal JB, van der Wees PJ, *et al*. Patient-centred physical therapy is (cost-) effective in increasing physical activity and reducing frailty in older adults with mobility problems: a randomized controlled trial with 6 months follow-up. *J Cachexia Sarcopenia Muscle* 2016;7:422–35.
- Groessl EJ, Kaplan RM, Castro Sweet CM, *et al*. Cost-effectiveness of the LIFE Physical activity intervention for older adults at increased risk for mobility disability. *J Gerontol A Biol Sci Med Sci* 2016;71:656–62.
- Owen L, Morgan A, Fischer A, *et al*. The cost-effectiveness of public health interventions. *J Public Health* 2012;34:37–45.
- Anokye NK, Trueman P, Green C, *et al*. Physical activity and health related quality of life. *BMC Public Health* 2012;12:624.
- Giné-Garriga M, Coll-Planas L, Guerra M, *et al*. The SITLESS project: exercise referral schemes enhanced by self-management strategies to battle sedentary behaviour in older adults: study protocol for a randomised controlled trial. *Trials* 2017;18:221.
- NICE. Physical activity: exercise referral schemes. 2014.
- van der Bij AK, Laurant MG, Wensing M. Effectiveness of physical activity interventions for older adults: a review. *Am J Prev Med* 2002;22:120–33.
- Chiang KC, Seman L, Belza B, *et al*. 'It is our exercise family': experiences of ethnic older adults in a group-based exercise program. *Prev Chronic Dis* 2008;5.
- Chang AK, Fritschi C, Kim MJ. Sedentary behavior, physical activity, and psychological health of Korean older adults with hypertension: effect of an empowerment intervention. *Res Gerontol Nurs* 2013;6:81–8.
- Morgan O. Approaches to increase physical activity: reviewing the evidence for exercise-referral schemes. *Public Health* 2005;119:361–70.
- Campbell F, Holmes M, Everson-Hock E, *et al*. A systematic review and economic evaluation of exercise referral schemes in primary care: a short report. *Health Technol Assess* 2015;19:1–110.
- Owen N, Sugiyama T, Eakin EE, *et al*. Adults' sedentary behavior determinants and interventions. *Am J Prev Med* 2011;41:189–96.
- Bauman AE, Reis RS, Sallis JF, *et al*. Correlates of physical activity: why are some people physically active and others not? *Lancet* 2012;380:258–71.
- Nour K, Laforest S, Gauvin L, *et al*. Behavior change following a self-management intervention for housebound older adults with arthritis: an experimental study. *Int J Behav Nutr Phys Act* 2006;3:12.
- Petrou S, Gray A. Economic evaluation alongside randomised controlled trials: design, conduct, analysis, and reporting. *BMJ* 2011;342:d1548.
- NICE. *Methods for the development of NICE public health guidance*. London: National Institute for Clinical Excellence, 2012.
- Husereau D, Drummond M, Petrou S, *et al*. Consolidated Health Economic Evaluation Reporting Standards (CHEERS)--explanation and elaboration: a report of the ISPOR health economic evaluation publication guidelines good reporting practices task force. *Value Health* 2013;16:231–50.
- Sculpher MJ, Pang FS, Manca A, *et al*. Generalisability in economic evaluation studies in healthcare: a review and case studies. *Health Technol Assess* 2004;8:1–192.
- Drummond M, Pang F. Transferability of economic evaluation results. Economic evaluation in healthcare: merging theory with practice. 2001.
- Drummond MF, Sculpher MJ, Claxton K, *et al*. *Methods for the economic evaluation of health care programmes*: Oxford university press, 2015.
- Euro-Qol-Group, 2015. The EQ-5D-5L User Guide 2015. http://www.euroqol.org/fileadmin/user_upload/Documenten/PDF/Folders_Flyers/EQ-5D-5L_UserGuide_2015.pdf
- University of Birmingham, 2016. ICECAP-O Secondary. <http://www.birmingham.ac.uk/research/activity/mds/projects/HaPS/HE/ICECAP/ICECAP-O/index.aspx>
- Sen A. *Choice, welfare and measurement*: Harvard University Press, 1997.
- Makai P, Looman W, Adang E, *et al*. Cost-effectiveness of integrated care in frail elderly using the ICECAP-O and EQ-5D: does choice of instrument matter? *Eur J Health Econ* 2015;16:437–50.
- Sørensen JB, Skovgaard T, Puggaard L. Exercise on prescription in general practice: a systematic review. *Scand J Prim Health Care* 2006;24:69–74.
- Szende A, Oppe M, Devlin N. *EQ-5D valuation sets: inventory, comparative review and user guide*: Springer, 2007.
- Badia X, Roset M, Herdman M, *et al*. A comparison of United Kingdom and Spanish general population time trade-off values for EQ-5D health states. *Med Decis Making* 2001;21:7–16.
- Karlsson JA, Nilsson JÅ, Neovius M, *et al*. National EQ-5D tariffs and quality-adjusted life-year estimation: comparison of UK, US and Danish utilities in south Swedish rheumatoid arthritis patients. *Ann Rheum Dis* 2011;70:2163–6.

52. NICE, 2017. Position statement on use of the EQ-5D-5L valuation set. Secondary position statement on use of the EQ-5D-5L valuation set. https://www.nice.org.uk/Media/Default/About/what-we-do/NICE-guidance/NICE-technology-appraisal-guidance/eq5d5l_nice_position_statement.pdf
53. van Hout B, Janssen MF, Feng YS, *et al*. Interim scoring for the EQ-5D-5L: mapping the EQ-5D-5L to EQ-5D-3L value sets. *Value Health* 2012;15:708–15.
54. Manca A, Hawkins N, Sculpher MJ. Estimating mean QALYs in trial-based cost-effectiveness analysis: the importance of controlling for baseline utility. *Health Econ* 2005;14:487–96.
55. Rivero-Arias O, Gray A. The multinational nature of cost-effectiveness analyses alongside multinational clinical trials. *Value Health* 2010;13:34–41.
56. Vemer P, Rutten-van Mólken MP. The road not taken: transferability issues in multinational trials. *Pharmacoeconomics* 2013;31:863–76.
57. Oppong R, Jowett S, Roberts TE. Economic evaluation alongside multinational studies: a systematic review of empirical studies. *PLoS One* 2015;10:e0131949.
58. Ramsey SD, Willke RJ, Glick H, *et al*. Cost-effectiveness analysis alongside clinical trials II—An ISPOR Good Research Practices Task Force report. *Value Health* 2015;18:161–72.
59. Glick HA, Doshi JA, Sonnad SS, *et al*. *Economic evaluation in clinical trials*. OUP: Oxford, 2014.
60. Harris T, Kerry SM, Victor CR, *et al*. A primary care nurse-delivered walking intervention in older adults: PACE (pedometer accelerometer consultation evaluation)—Lift cluster randomised controlled trial. *PLoS Med* 2015;12:e1001783.
61. Pang F. Design, analysis and presentation of multinational economic studies: the need for guidance. *Pharmacoeconomics* 2002;20:75–90.
62. Manca A, Sculpher MJ, Goeree R. The analysis of multinational cost-effectiveness data for reimbursement decisions: a critical appraisal of recent methodological developments. *Pharmacoeconomics* 2010;28:1079–96.
63. Rice N, Jones A. Multilevel models and health economics. *Health Econ* 1997;6:561–75.
64. Adalsteinsson E, Toumi M. Benefits of probabilistic sensitivity analysis - a review of NICE decisions. *J Mark Access Health Policy* 2013;1:21240.
65. Woods B, Revill P, Sculpher M, *et al*. Country-level cost-effectiveness thresholds: initial estimates and the need for further research. *Value Health* 2016;19:929–35.
66. Ramsey S, Willke R, Briggs A, *et al*. Good research practices for cost-effectiveness analysis alongside clinical trials: the ISPOR RCT-CEA task force report. *Value Health* 2005;8:521–33.
67. Oostenbrink JB, Al MJ, Mj A. The analysis of incomplete cost data due to dropout. *Health Econ* 2005;14:763–76.
68. Faria R, Gomes M, Epstein D, *et al*. A guide to handling missing data in cost-effectiveness analysis conducted within randomised controlled trials. *Pharmacoeconomics* 2014;32:1157–70.
69. Frew EJ, Bhatti M, Win K, *et al*. Cost-effectiveness of a community-based physical activity programme for adults (Be Active) in the UK: an economic analysis within a natural experiment. *Br J Sports Med* 2014;48:207–12.
70. Roux L, Pratt M, Tengs TO, *et al*. Cost effectiveness of community-based physical activity interventions. *Am J Prev Med* 2008;35:578–88.
71. Ekelund U, Steene-Johannessen J, Brown WJ, *et al*. Does physical activity attenuate, or even eliminate, the detrimental association of sitting time with mortality? A harmonised meta-analysis of data from more than 1 million men and women. *The Lancet* 2016;388:1302–10.
72. Glynn NW, Santanasto AJ, Simonsick EM, *et al*. The pittsburgh fatigability scale for older adults: development and validation. *J Am Geriatr Soc* 2015;63:130–5.