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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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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 three-armed pragmatic randomised controlled trial (RCT). Healthcare costs (hospitalisations, accident and emergency visits, appointment with health professionals) and social care costs (e.g. 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 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.

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.

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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,3 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 populations14–15 or to a population with specific chronic conditions.16–18 Only few focus on older adults19–21 without major health conditions20,21 with specific chronic conditions19,22,23 or mobility problems.24–25

A review carried out by Owen et al26 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 al13 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.25 Pavé et al24 found that ERS interventions were cost-effective only in inactive but healthy populations,10 de Vries et al24 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.29

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.1426 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 SB20 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 fulfill 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 practices; 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 and personal social services perspective as recommended by UK’s NICE guidelines. 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, 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-5L and capability well-being estimated using the ICECap Measure for Older People (ICECAP-O). 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 theory), thus incorporating both health and non-health dimensions.

**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.

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

Deidda M, et al. BMJ Open 2018;8:e022266. doi:10.1136/bmjopen-2018-022266
might significantly affect CUA.\textsuperscript{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,\textsuperscript{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.\textsuperscript{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.\textsuperscript{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 intervention) might be calculated as a proportion of available cost data.

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

ERS, exercise referral scheme; ICECAP-O, ICEpop Capability Measure for Older People; PA, physical activity; QALY, quality-adjusted life-years; SB, sedentary behaviour.
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 per cent 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 effects\(^{67}\)).

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

| Cost component                                      | Timing of collection                                                                 | Source of data            | Multicountry-specific issues                                      |
|-----------------------------------------------------|--------------------------------------------------------------------------------------|---------------------------|-------------------------------------------------------------------|
| ERS; usual care; ERS+SMS                            | Use of exercise services                                                            | Patient Resource Use Questionnaire |                                                                    |
|                                                     | Visits to exercise facilities                                                       | Patient Resource Use Questionnaire |                                                                    |
|                                                     | Opportunity cost of walking/exercise                                                 | Patient Resource Use Questionnaire |                                                                    |
|                                                     | Community costs (use of social services)                                            | Patient Resource Use Questionnaire | Use of country-specific examples                                   |
|                                                     | National health system costs (use of health services)                                | Patient Resource Use Questionnaire | Specify if covered by national health system; private insurance; copayment; herself/himself |
|                                                     | Visits (eg, GP, nurses, physiotherapist)                                            | Patient Resource Use Questionnaire |                                                                    |
|                                                     | Overnight hospital stays                                                            | Patient Resource Use Questionnaire |                                                                    |
|                                                     | Medication (prescribed and non-prescribed)                                          | 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           | Patient Resource Use Questionnaire |                                                                    |
|                                                     | Personal costs related to improvement of health/reduction of sedentary behaviour     | Patient Resource Use Questionnaire |                                                                    |
|                                                     | Costs related to falls (falls requiring medical care/hospital admission)             | Patient Resource Use Questionnaire |                                                                    |
|                                                     | ERS/UC delivery cost                                                                | ERS and UC intervention cost log |                                                                    |
|                                                     | Primary care/community (SMS service delivery costs)                                 | SMS intervention cost log |                                                                    |
|                                                     |                                                                                     |                           |                                                                    |

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

### Missing data
Following best practice, 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. 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 NICE\textsuperscript{29} guidelines. As noted by Pavey et al.,\textsuperscript{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.\textsuperscript{49} and Roux et al.\textsuperscript{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.\textsuperscript{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.\textsuperscript{80}

**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.\textsuperscript{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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**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-20150018) (University of Southern Denmark, Denmark), Office for Research Ethics Committees in Northern Ireland (ORECNI reference number: 16/NI/01165) (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.

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